

FIG. 1

		P22		Y91						L265	
Class I	HDLP	P	L	G	G	Y	E	N	P	Y	L
	HDAC1	P	M	G	-	E	D	C	P	R	L
	HDAC2	P	M	G	-	E	D	C	P	R	L
	HDAC3	P	M	G	-	D	D	C	P	R	L
	HDAC8	A	K	G	-	Y	D	C	P	P	M
Class II	HDAC4	P	E	G	V	D	S	D	T	P	L
	HDAC5	P	E	G	V	D	S	D	T	P	L
	HDAC6(a)	P	E	-	-	-	-	D	S	P	K
	HDAC6(b)	P	E	-	-	-	-	D	S	P	L
	HDAC7	P	E	G	G	D	T	D	T	P	L

FIG. 2

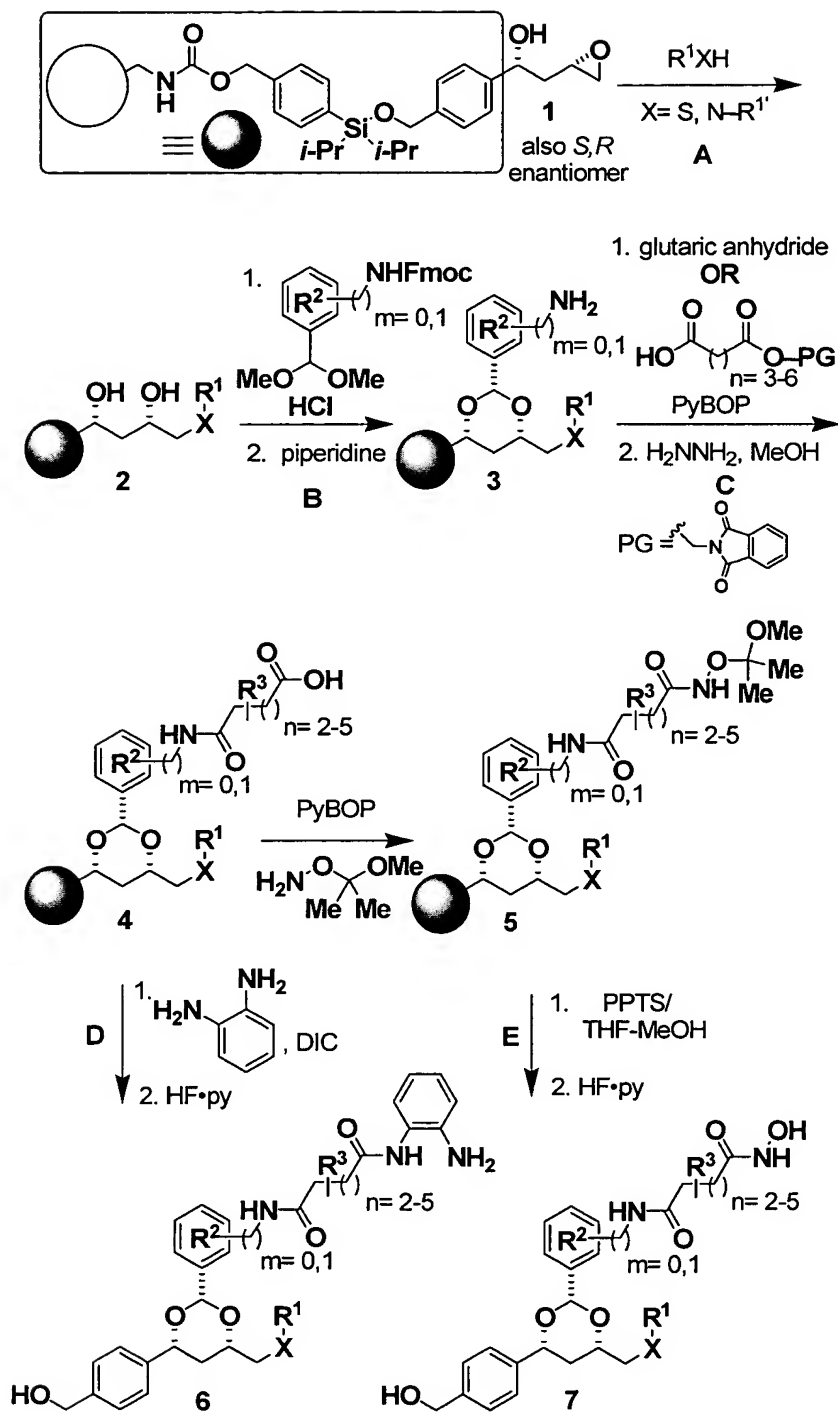
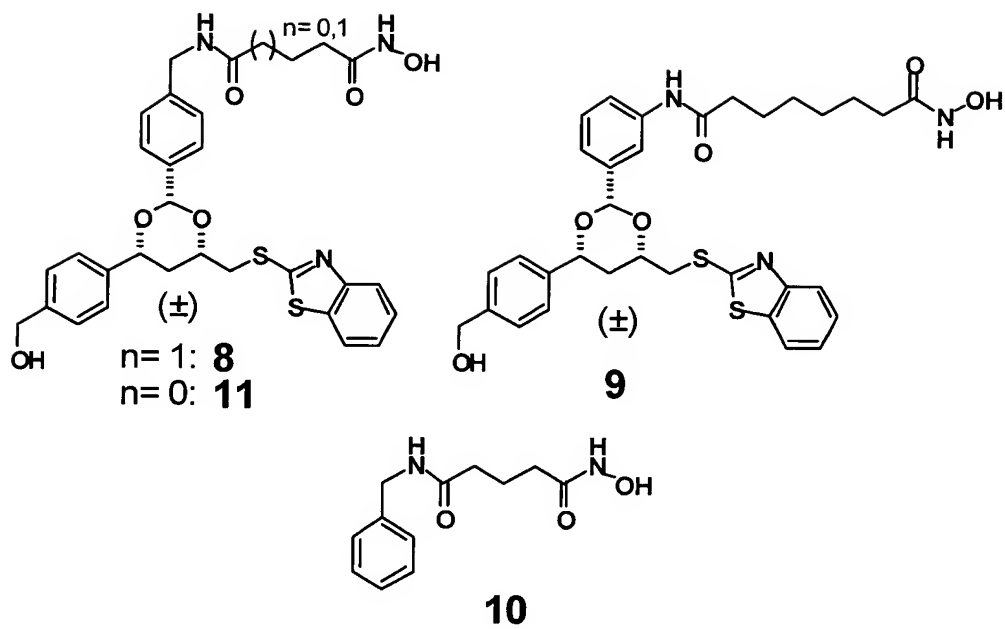


FIG. 3

Compound	HDAC1	HDAC6
8	1.2 ± 0.5	0.9 ± 0.2
9	1.7 ± 1.2	1.1 ± 0.1
10	1.5 ± 0.2	0.38 ± 0.04

FIG. 4

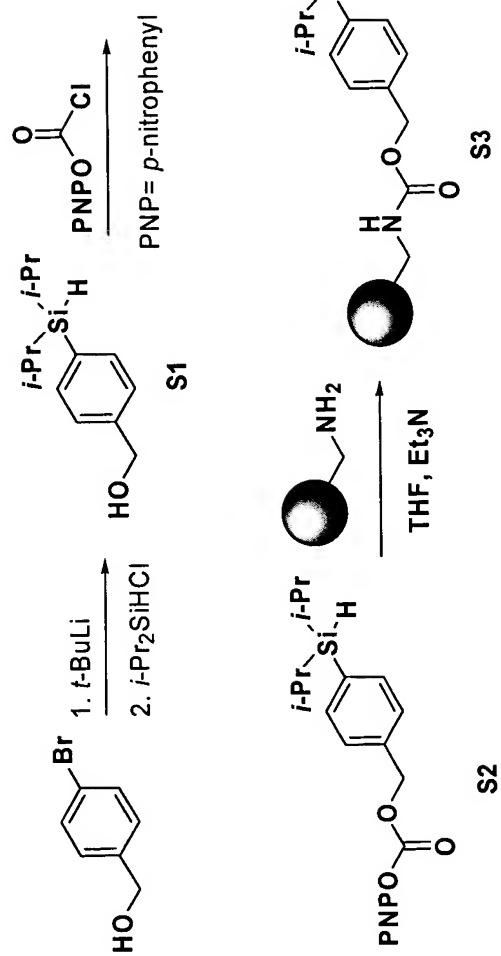


FIG. 5

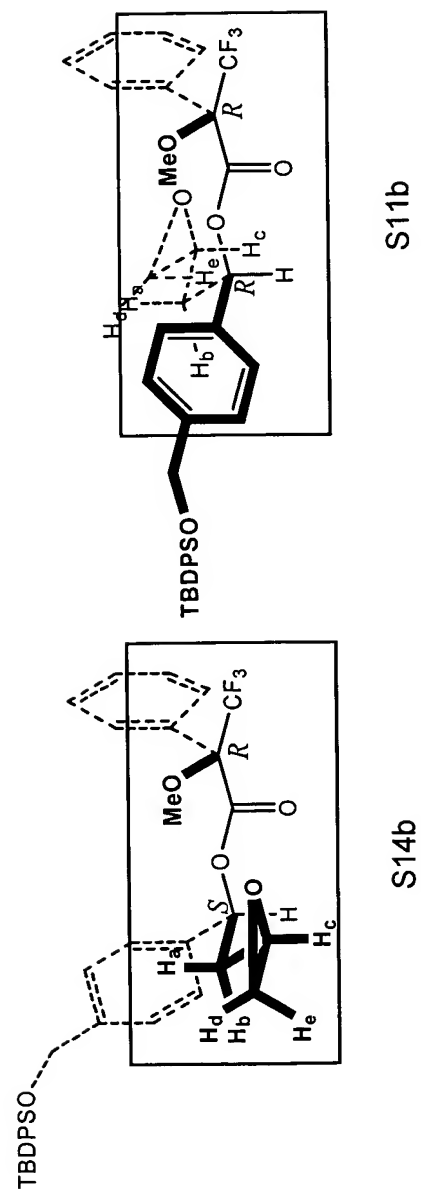


FIG. 6

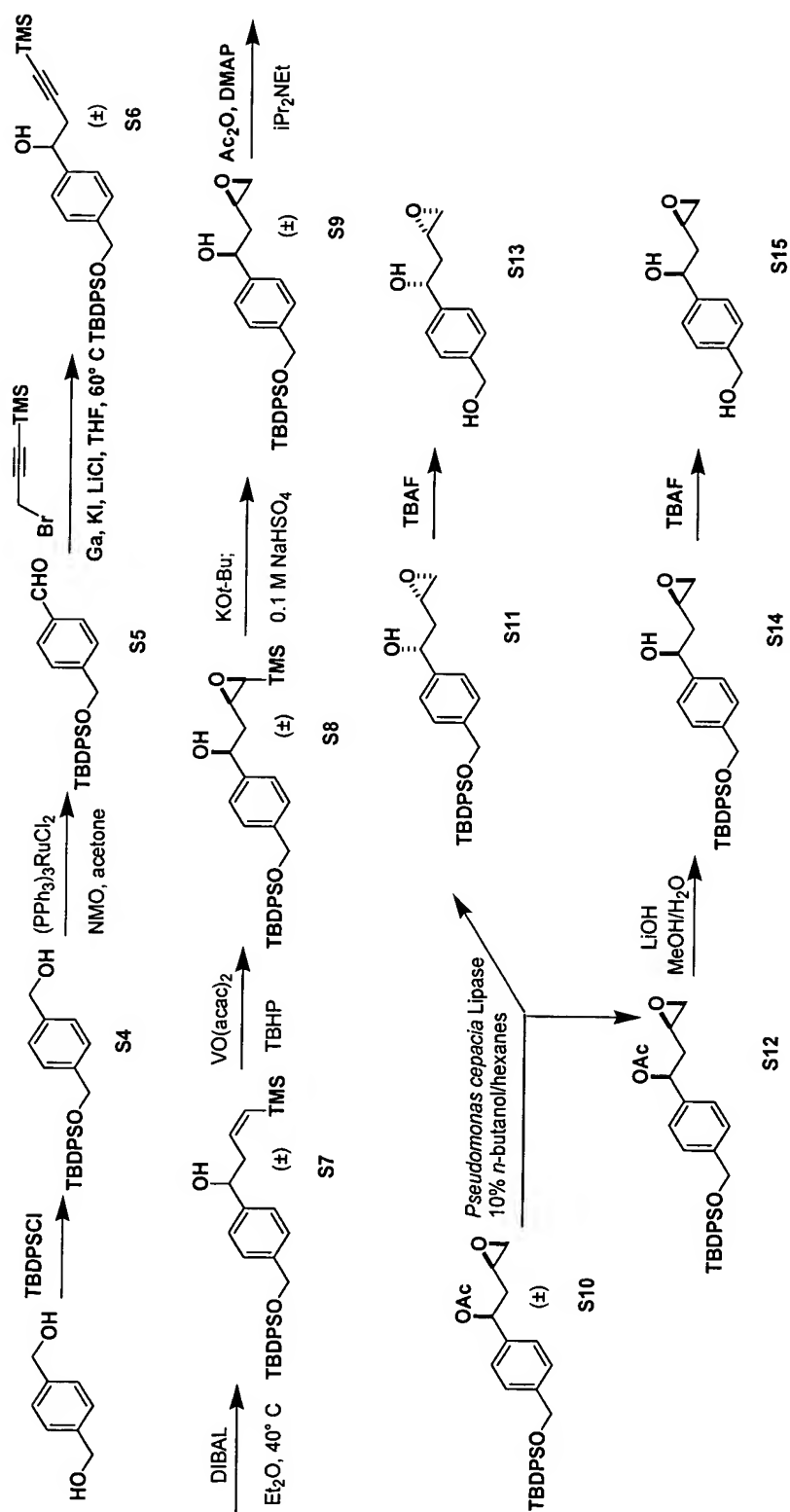


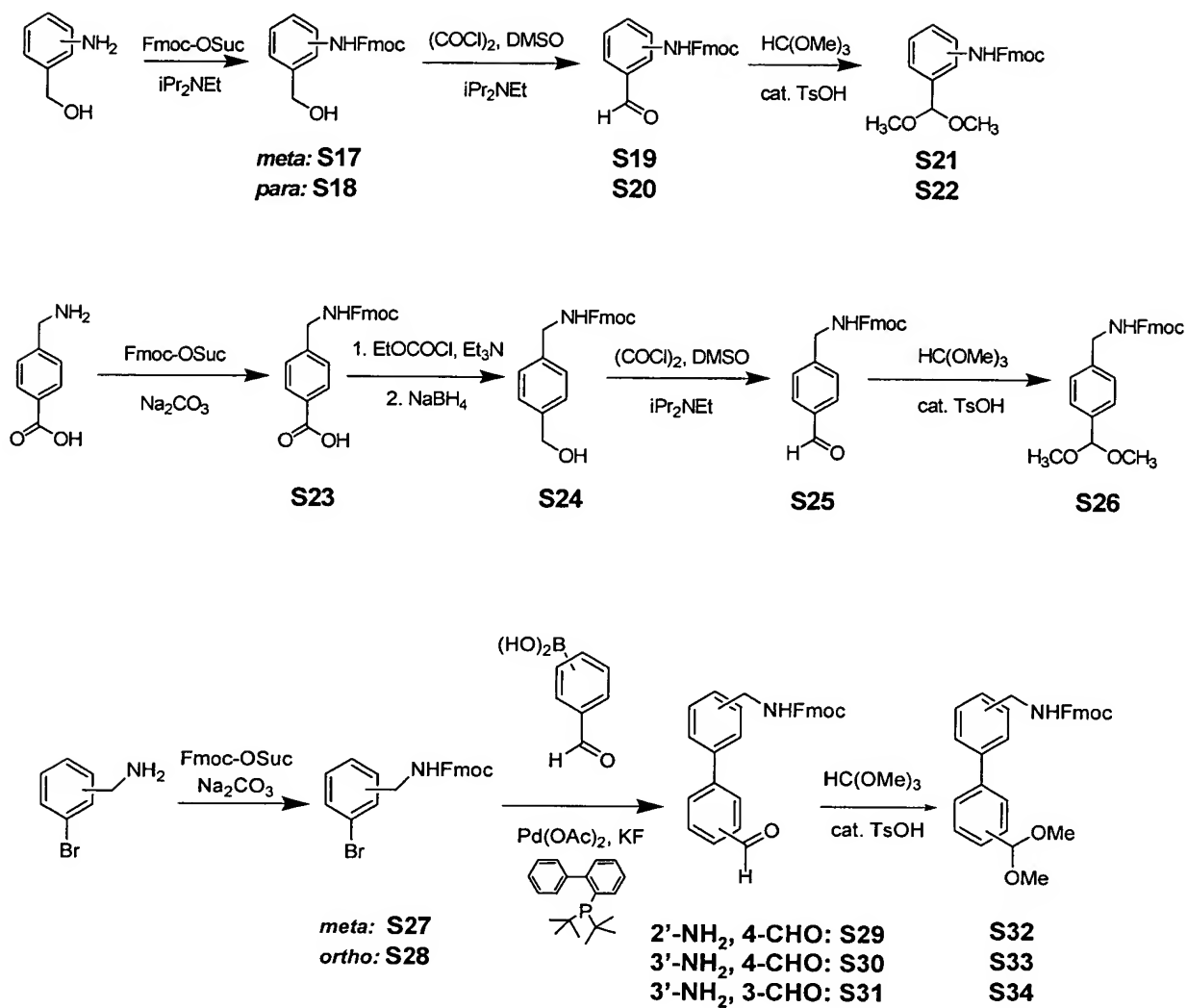
FIG. 7

FIG. 8A



FIG. 8B

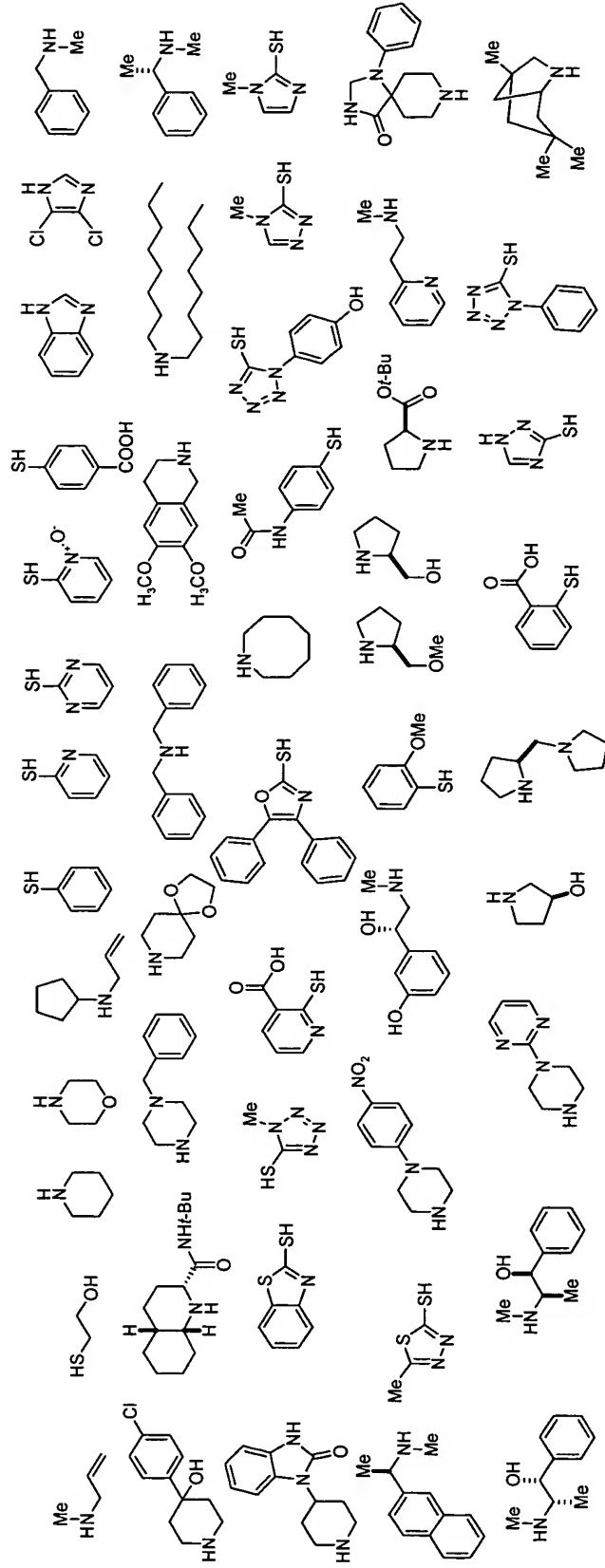
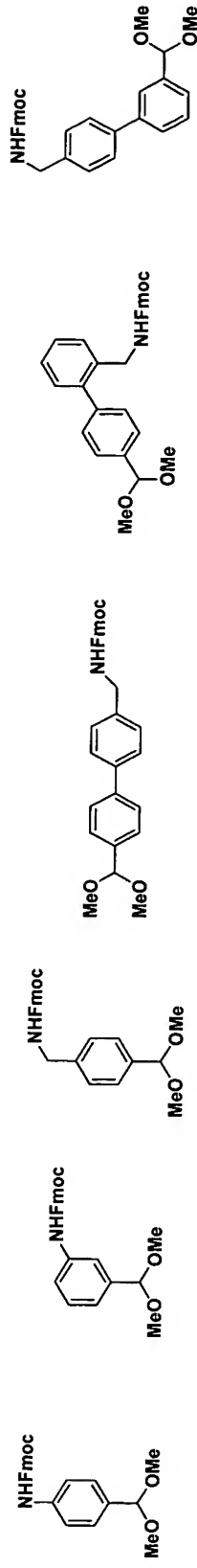


FIG. 8C



8/78

FIG. 8D

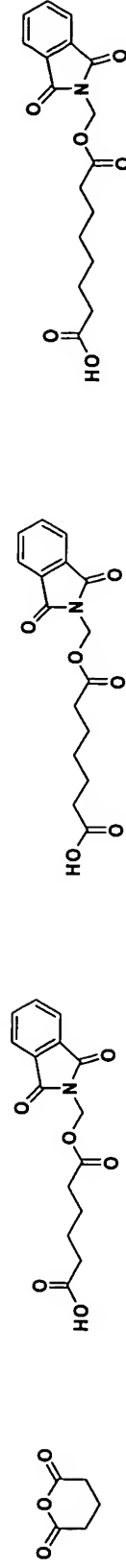


FIG. 9A

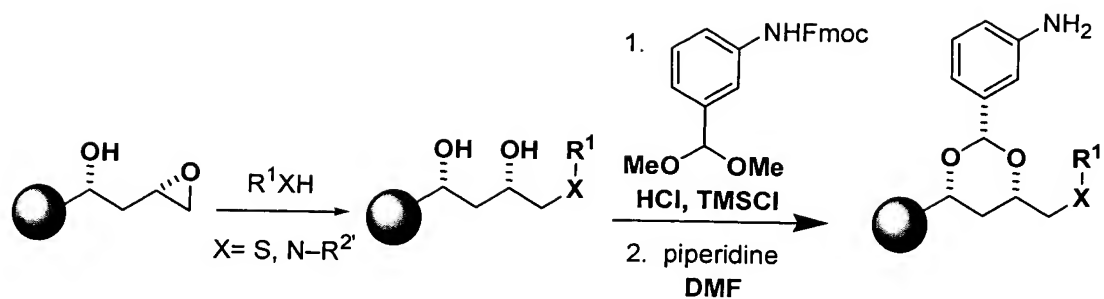


FIG. 9B

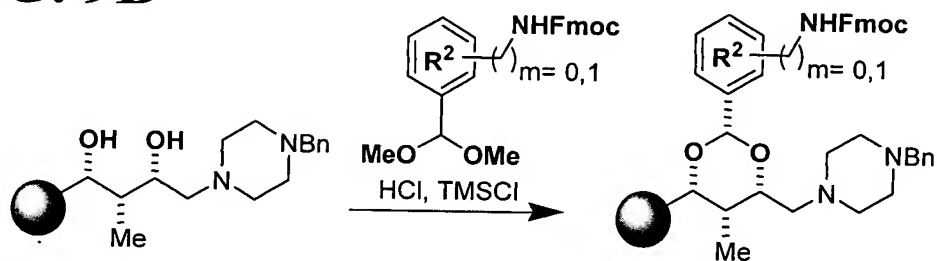
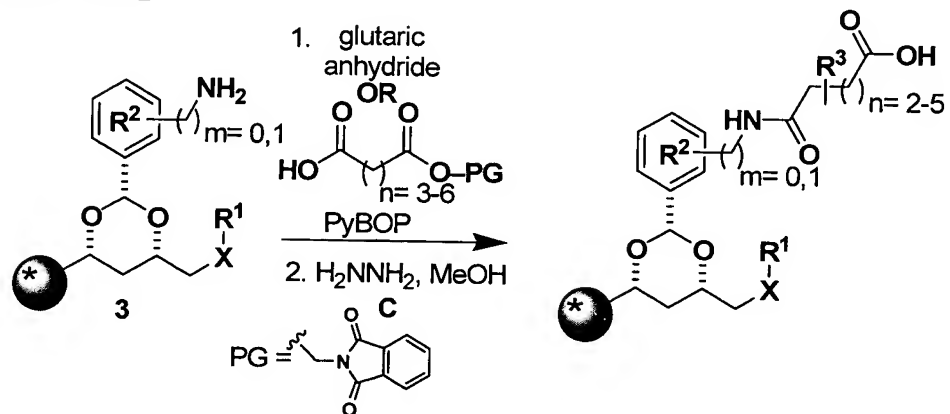


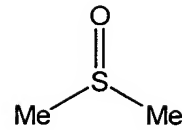
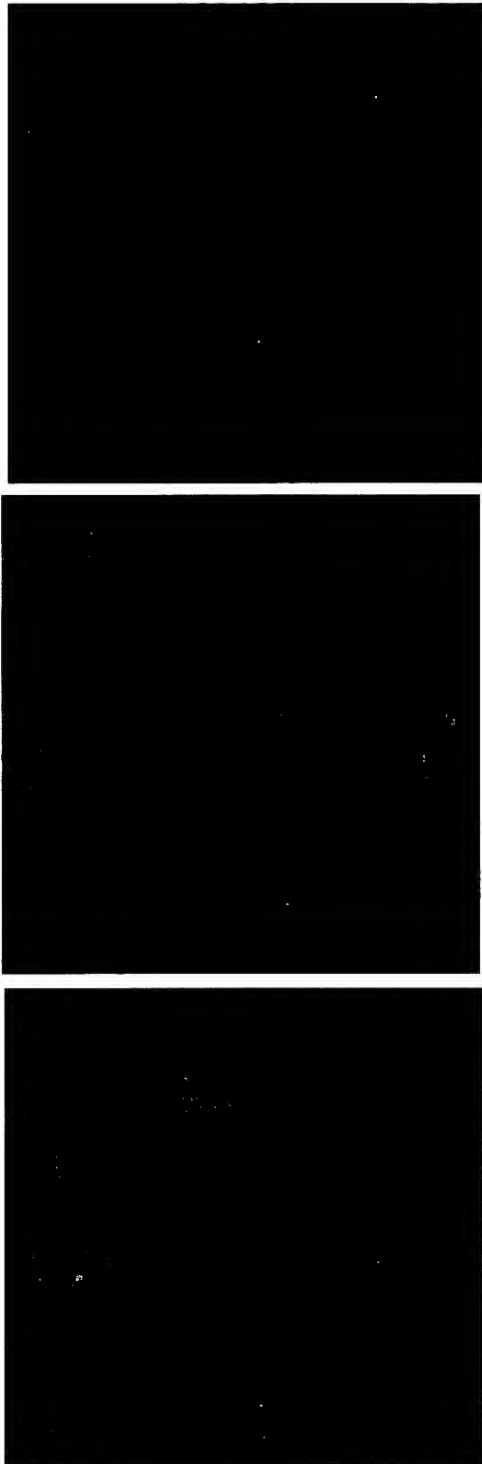
FIG. 9C



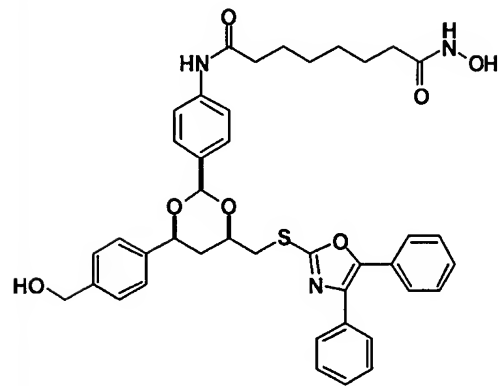
10/78

FIG. 10

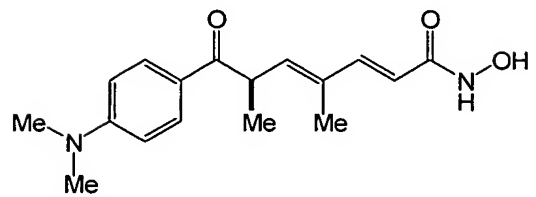
Glutaraldehyde/TX-100 fixation



Dimethylsulfoxide (0.1%)



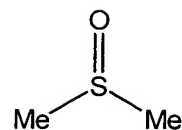
JCWII144 (200 nM)



trichostatin (100 nM)

FIG. 11

95% ethanol/5% acetic acid fixation



Dimethylsulfoxide (0.1%)

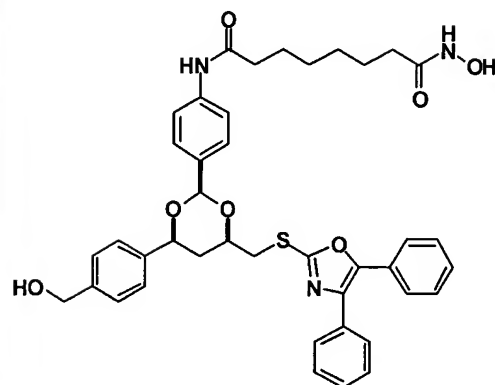
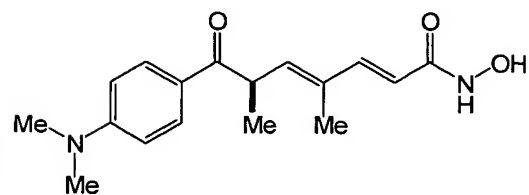
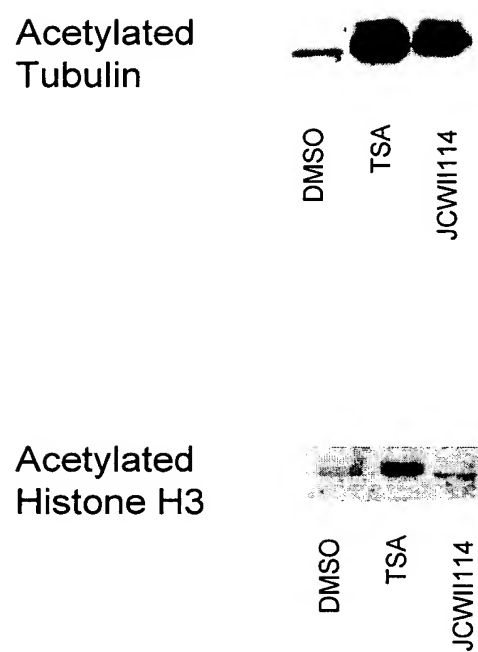
JCWII144 (2 μ M)trichostatin (1 μ M)

FIG. 12

Notes:

TSA treatment at 300nM

JCWII114 treatment at 2 μ M

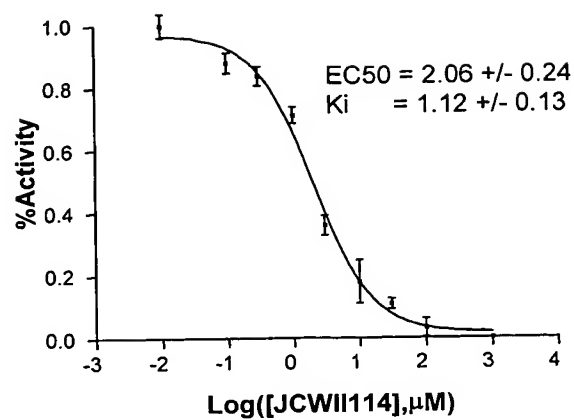
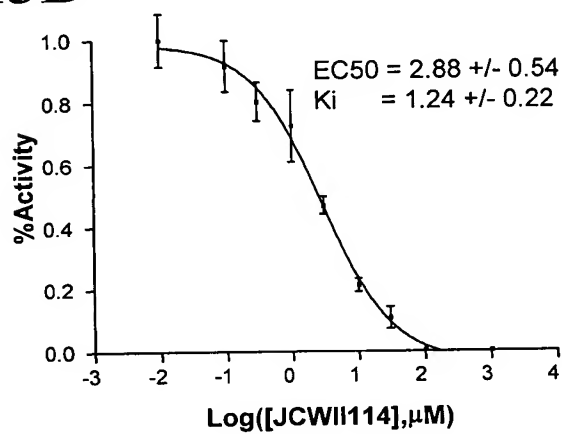
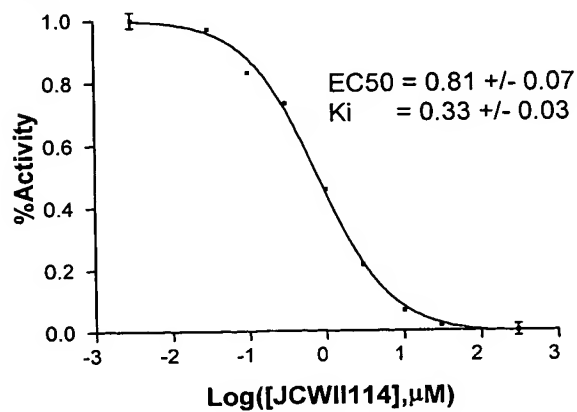
FIG. 13A**FIG. 13B****FIG. 13C**

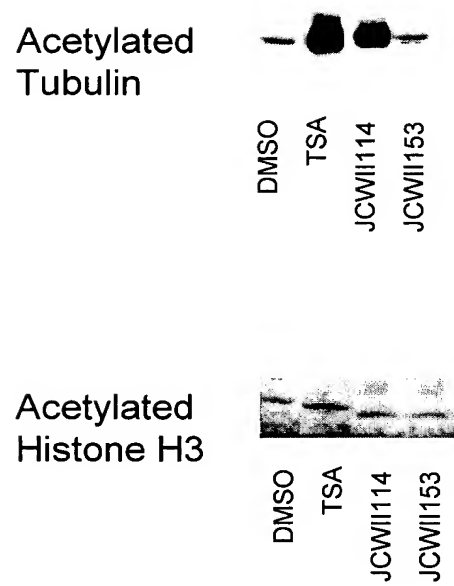
FIG. 14

FIG. 15

DMSO	TSA (200 nM)
JCWII114 (2 μ M)	JCWII153 (2 μ M)
JCWII169 (2 μ M)	JCWII169 (20 μ M)

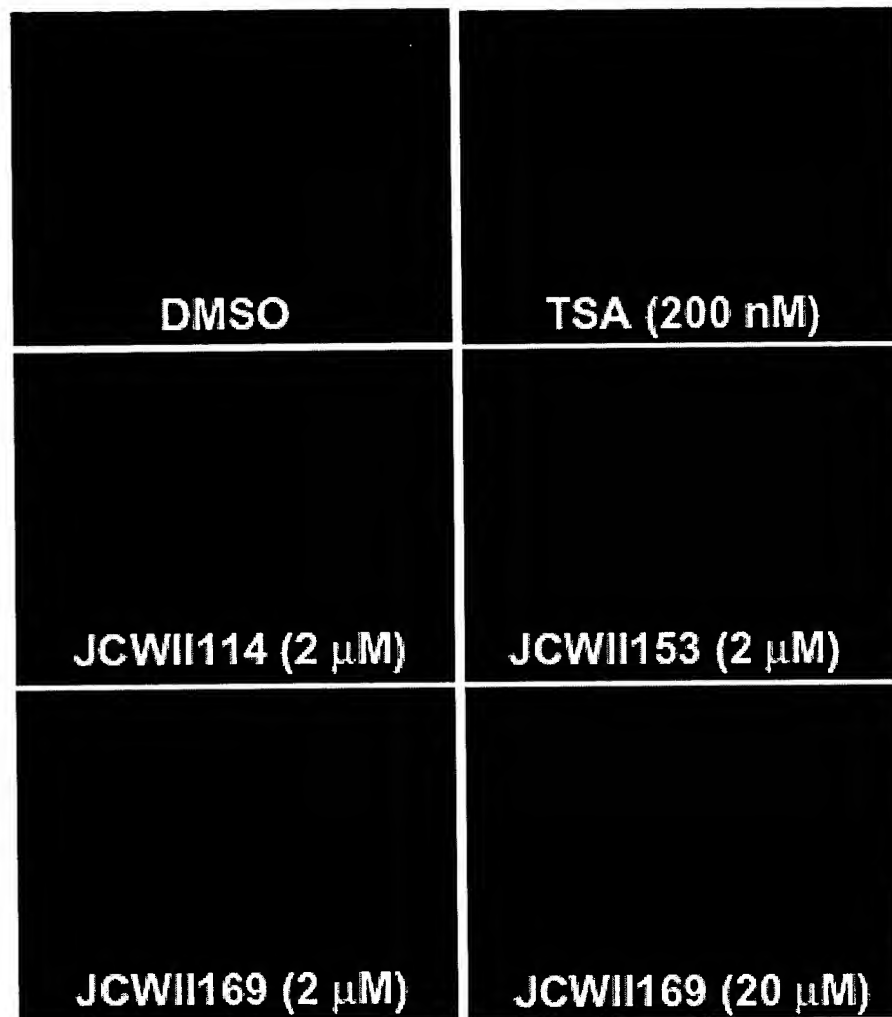
FIG. 16

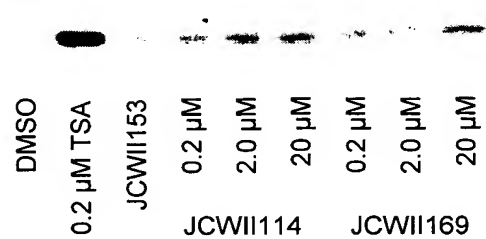
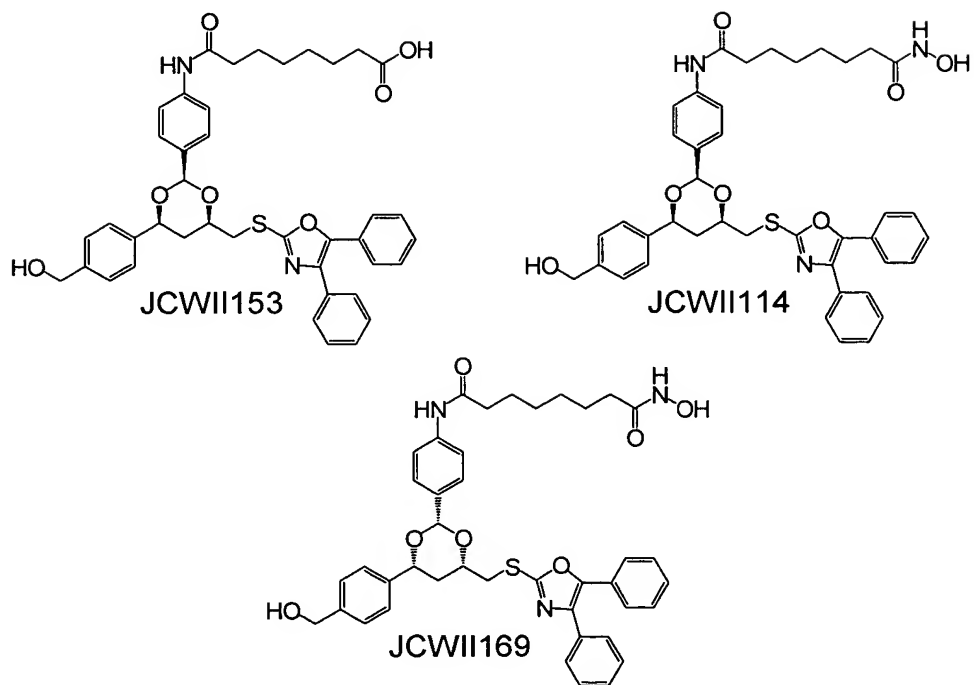
FIG. 17A**FIG. 17B****FIG. 17C**

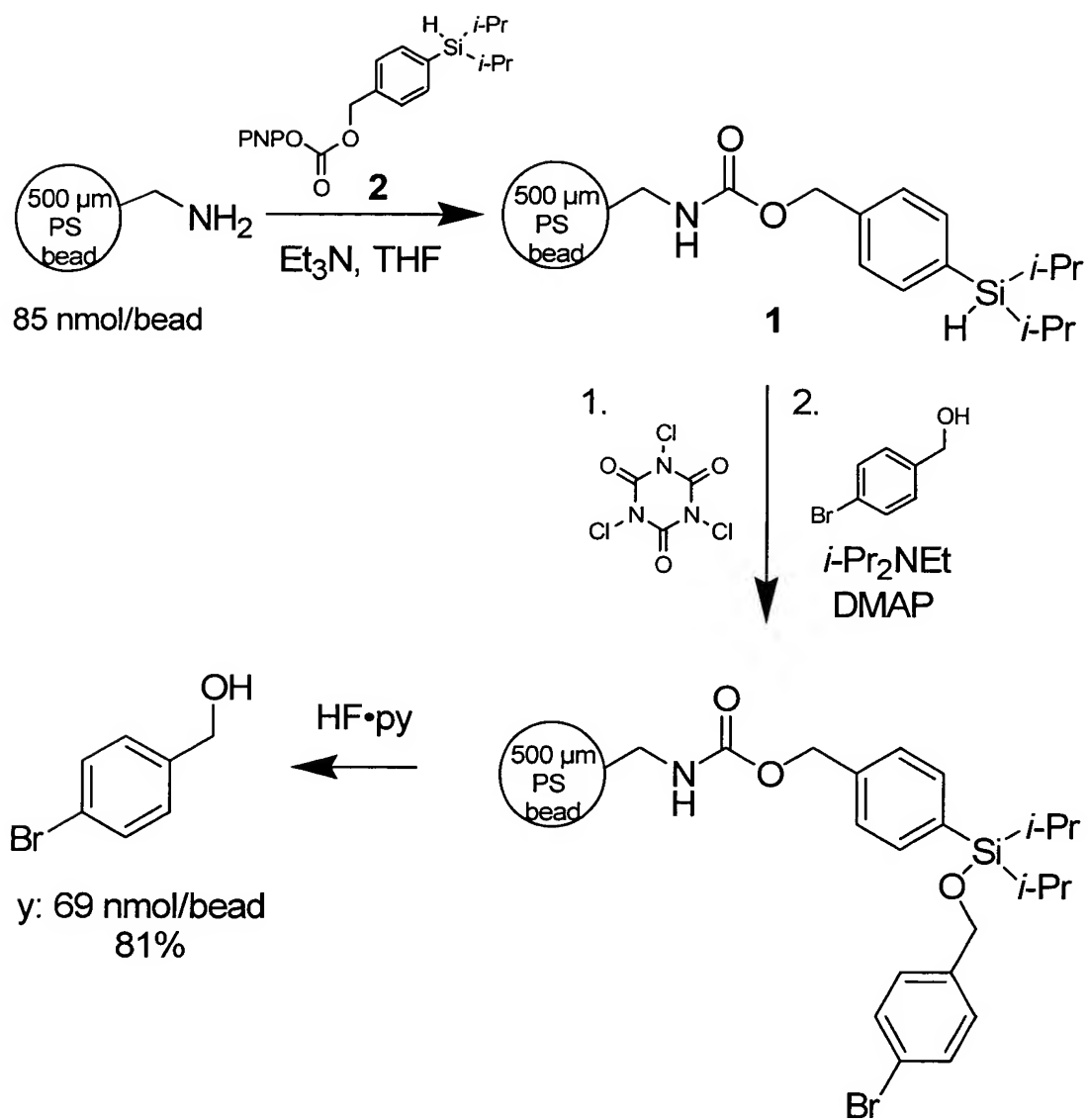
FIG. 18

FIG. 19

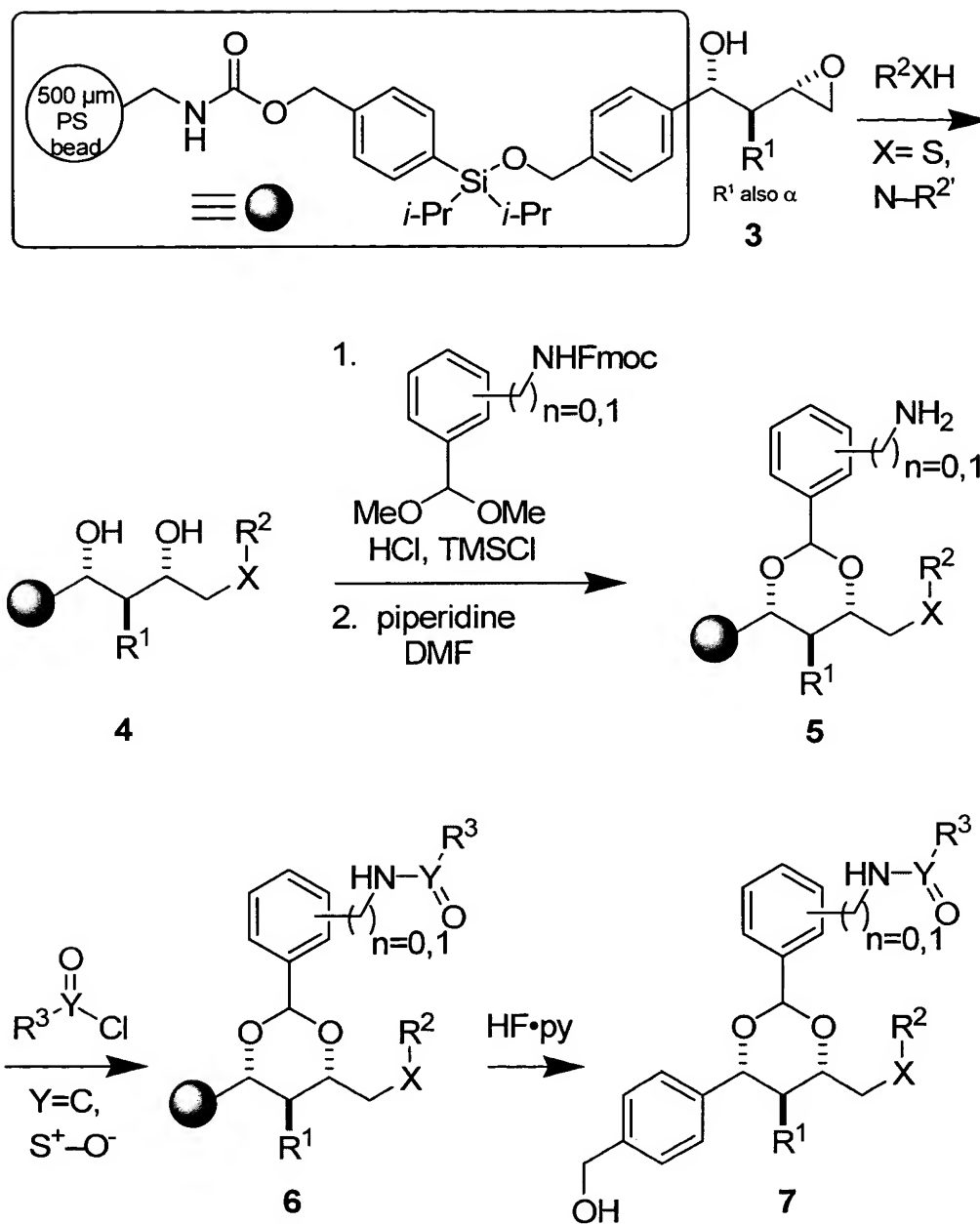


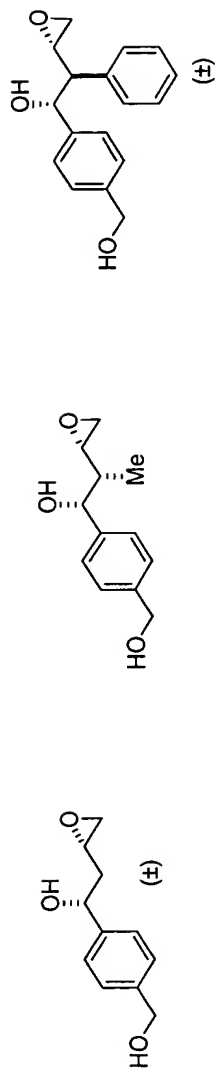
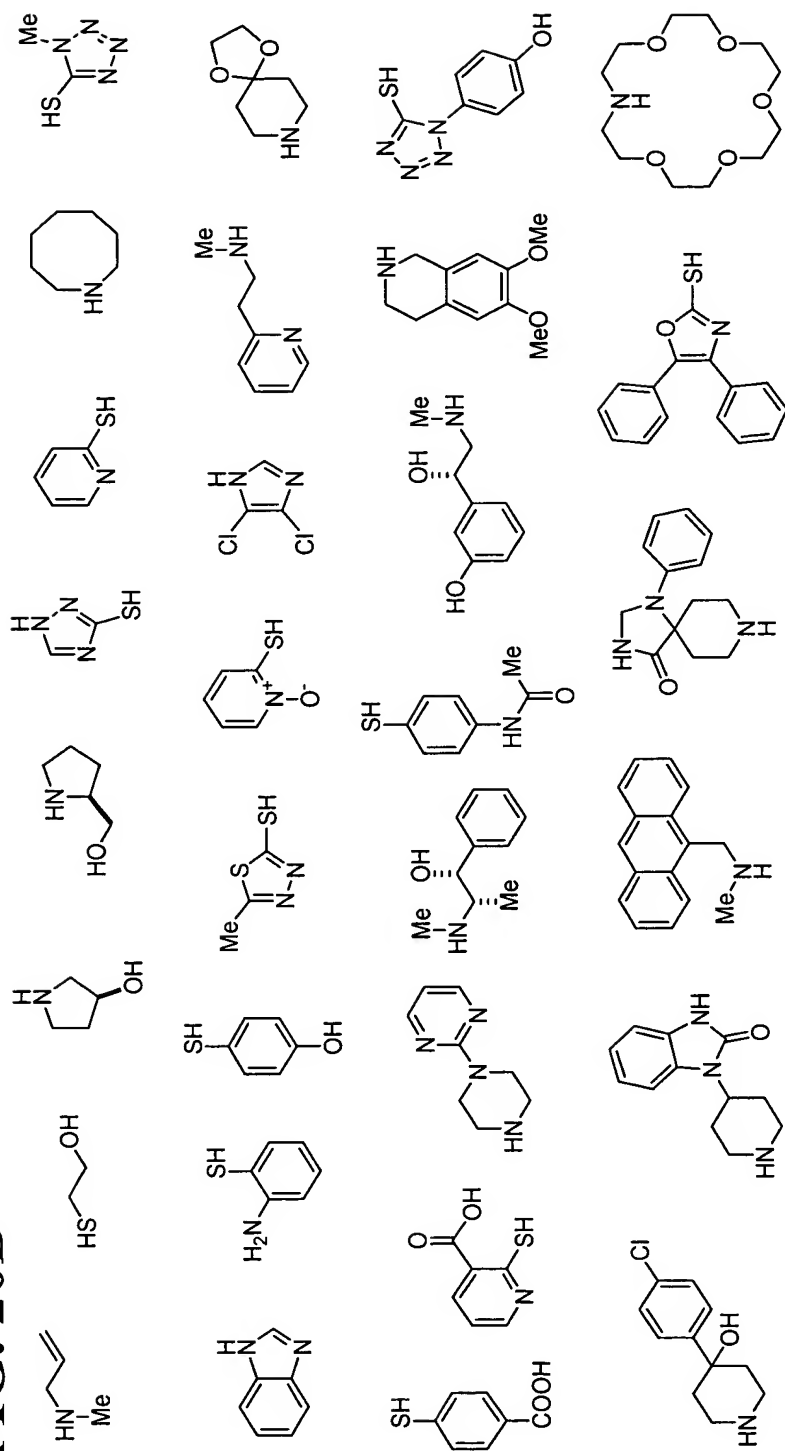
FIG. 20A**FIG. 20B**

FIG. 20C

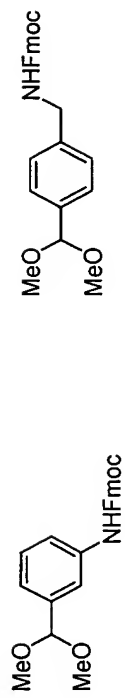


FIG. 20D

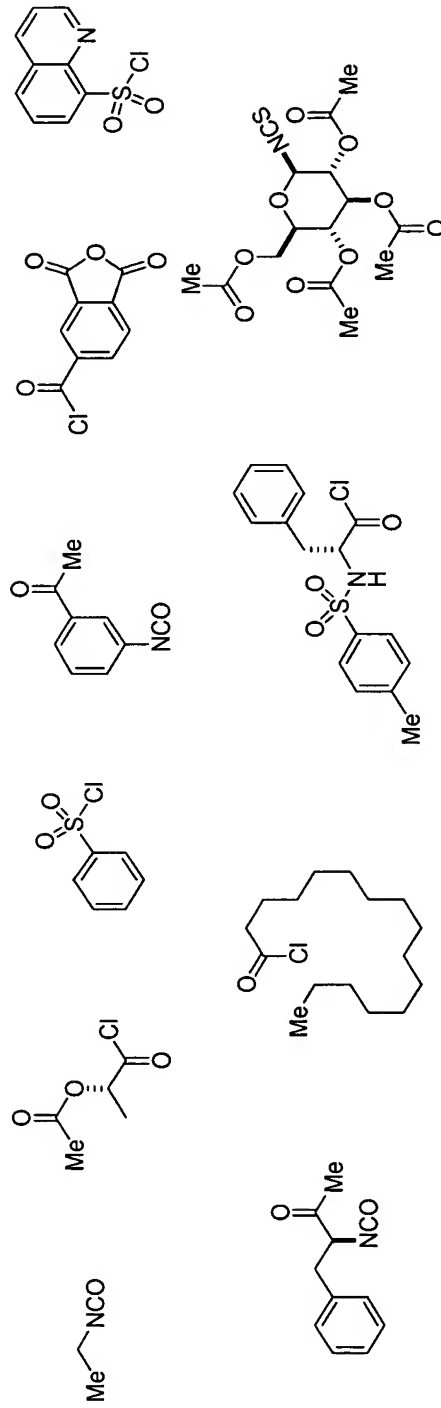
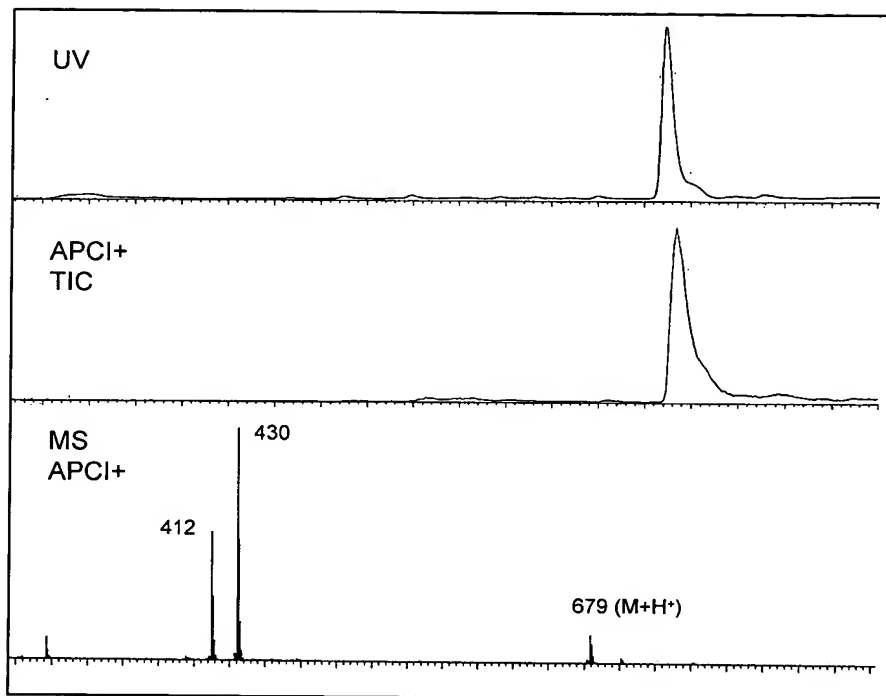


FIG. 21A

↓
To FIG. 21B

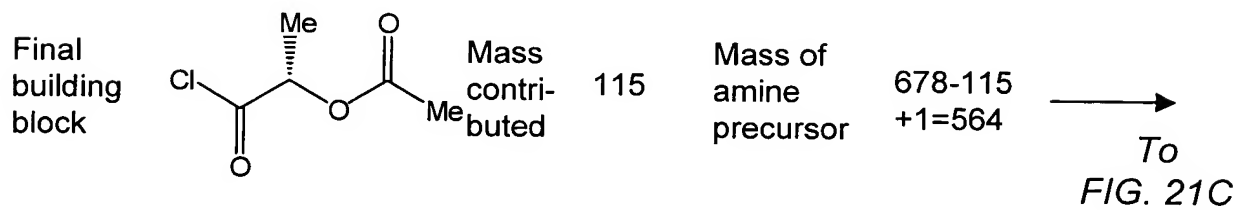
FIG. 21B

FIG. 21C

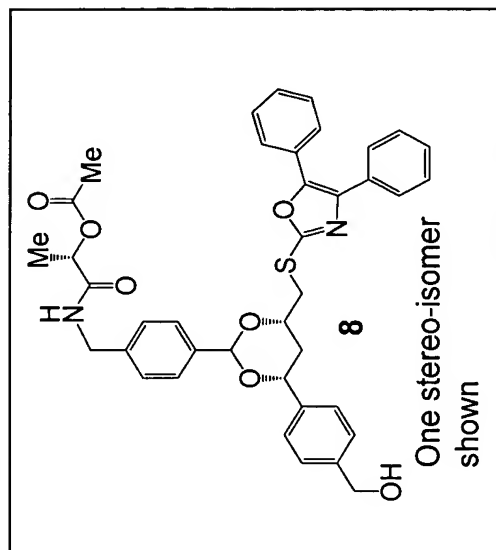
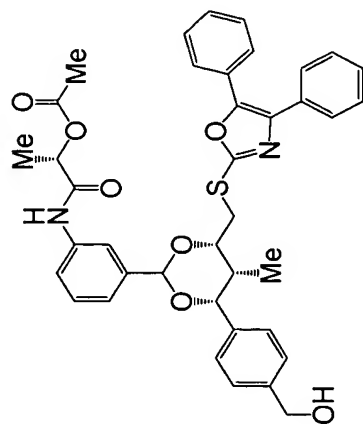
	acetal fragment	3-epoxy alcohols			acetal fragment	3-epoxy alcohols		
	103	194	208	270	117	194	208	270
30 nucleophiles	71	368	382	444	71	382	396	458
	78	375	389	451	78	389	403	465
	87	384	398	460	87	398	412	474
	101	398	412	474	101	412	426	488
	101	398	412	474	101	412	426	488
	111	408	422	484	111	422	436	498
	113	410	424	486	113	424	438	500
	116	413	427	489	116	427	441	503
	118	415	429	491	118	429	443	505
	125	422	436	498	125	436	450	512
	126	423	437	499	126	437	451	513
	127	424	438	500	127	438	452	514
	132	429	443	505	132	443	457	519
	136	433	447	509	136	447	461	523
	136	433	447	509	136	447	461	523
	143	440	454	516	143	454	468	530
	154	451	465	527	154	465	479	541
	155	452	466	528	155	466	480	542
	164	461	475	537	164	475	489	551
	165	462	476	538	165	476	490	552
	167	464	478	540	167	478	492	554
	167	464	478	540	167	478	492	554
	193	490	504	566	193	504	518	580
	194	491	505	567	194	505	519	581
	211	508	522	584	211	522	536	598
	217	514	528	590	217	528	542	604
	221	518	532	594	221	532	546	608
	231	528	542	604	231	542	556	618
	253	550	564	626	253	564	578	640
	263	560	574	636	263	574	588	650



To
FIG. 21D

FIG. 21D

possible structures



To FIG. 21E

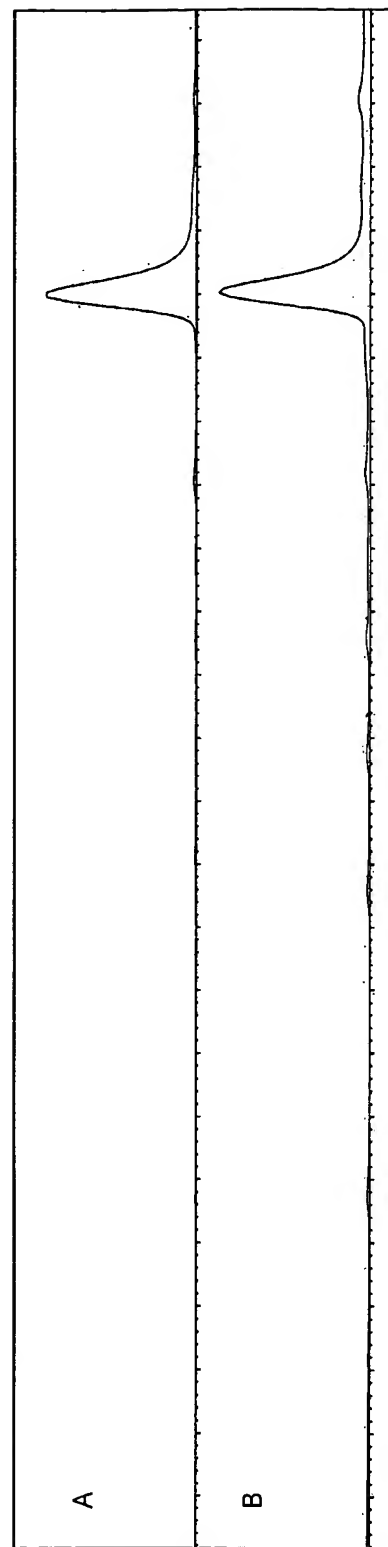
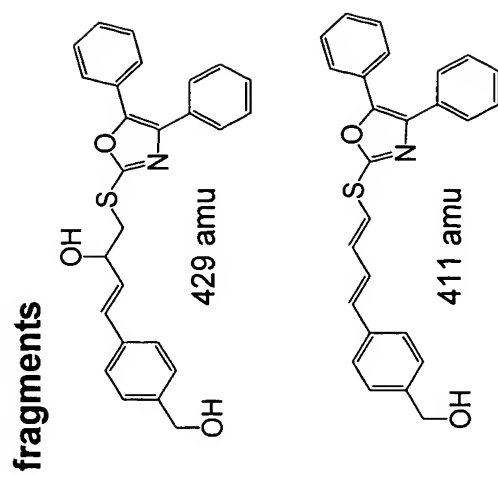
FIG. 21E

FIG. 22A

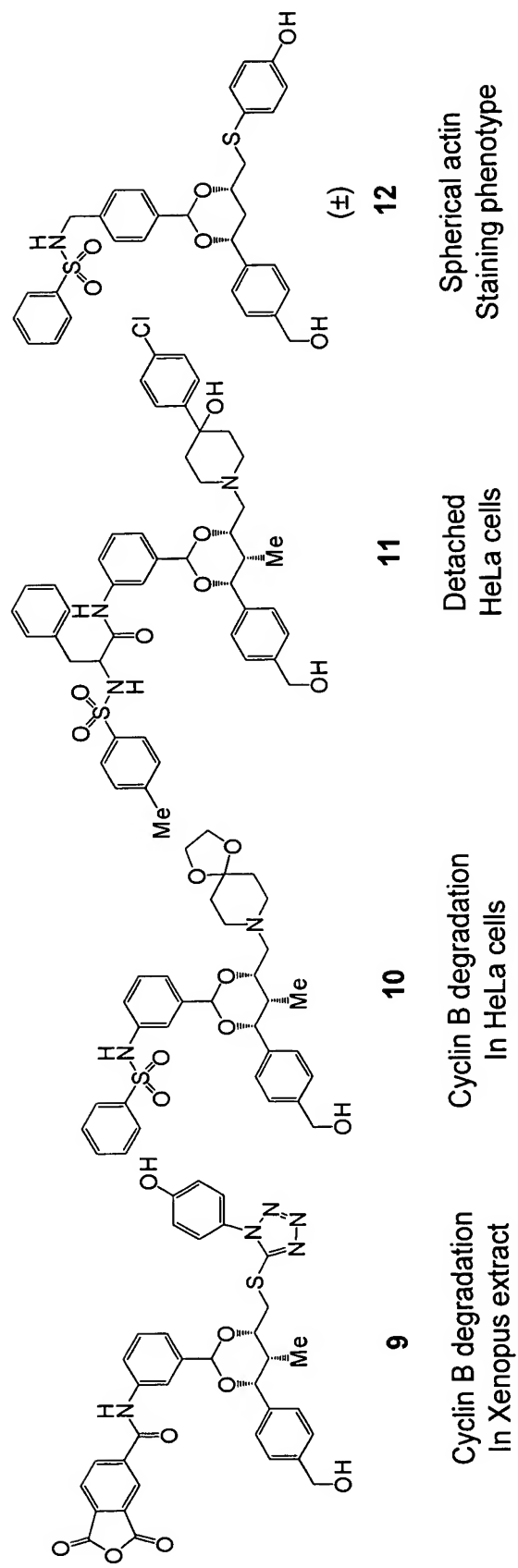
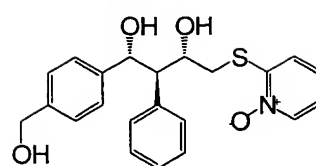
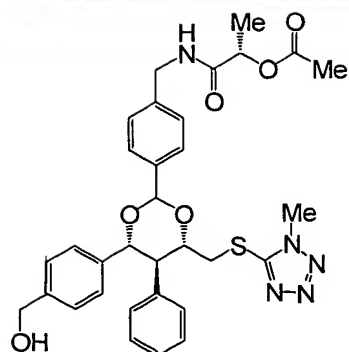
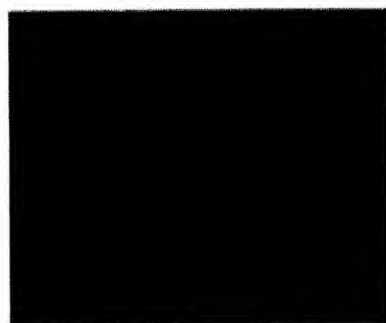


FIG. 22B

No compound

60 μ M
24h

(±)

13**FIG. 22C****14**

One stereoisomer shown

FIG. 23A

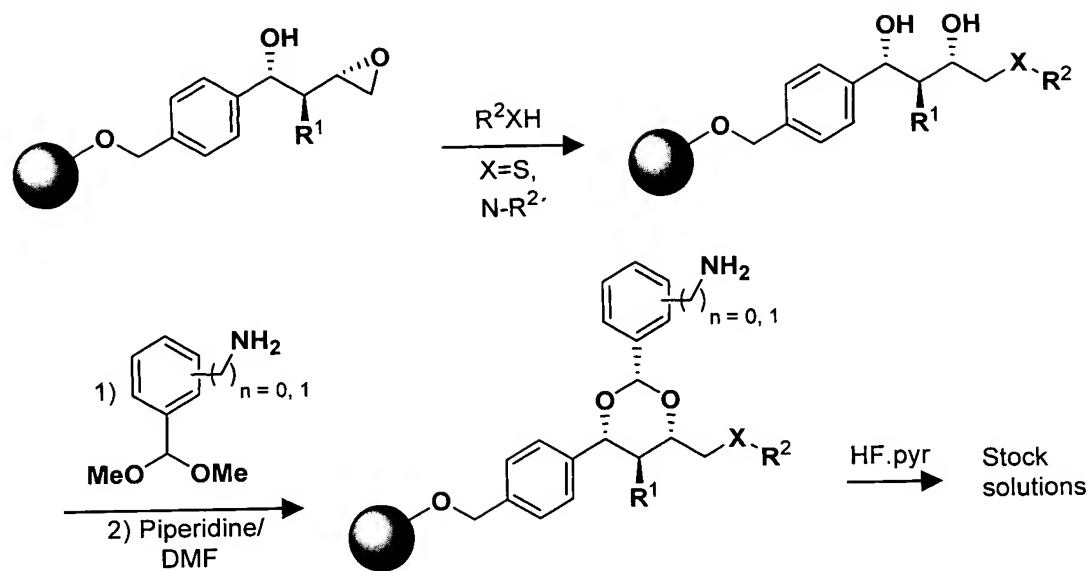


FIG. 23B

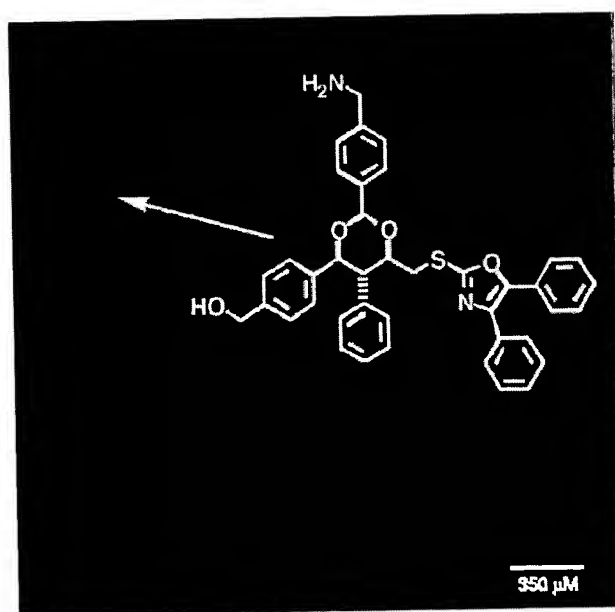


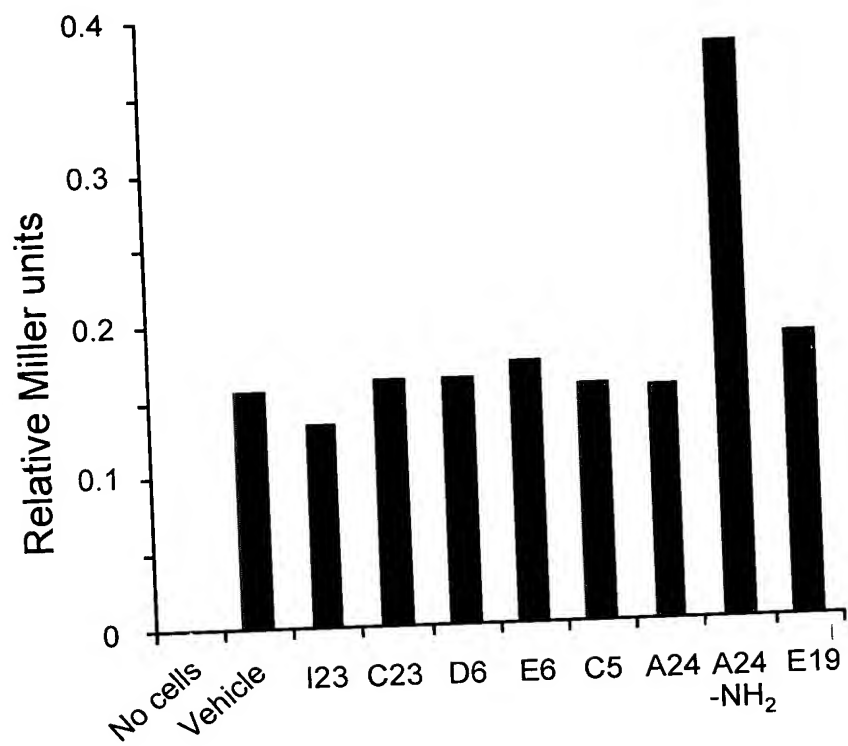
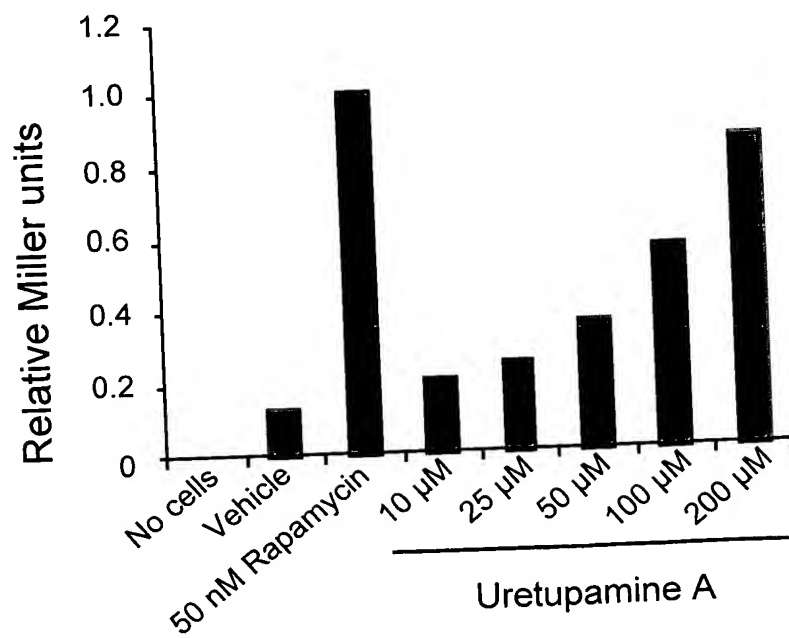
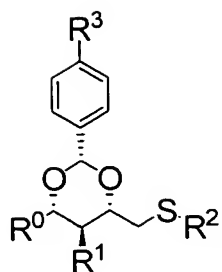
FIG. 24A**FIG. 24B**

FIG. 24C

Uretupamine	R^0	R^1	R^2	R^2	Activity
A	$HOCH_2-4-Ph$	Ph	2-MDPO	CH_2NH_2	56
B	$HOCH_2-4-Ph$	H	2-MDPO	CH_2NH_2	105
C	$HOCH_2-4-Ph$	$(\beta)-CH_3$	2-MDPO	CH_2NH_2	41*
D	$HOCH_2-4-Ph$	H	Ph	CH_2NH_2	7
E	$HOCH_2-4-Ph$	H	2-MBO	CH_2NH_2	10
F	$HOCH_2-4-Ph$	H	2-MDPO	H	14
G	$HOCH_2-4-Ph$	H	2-MDPO	CH_2NHAc	16
H	H	H	2-MDPO	CH_2NH_2	13

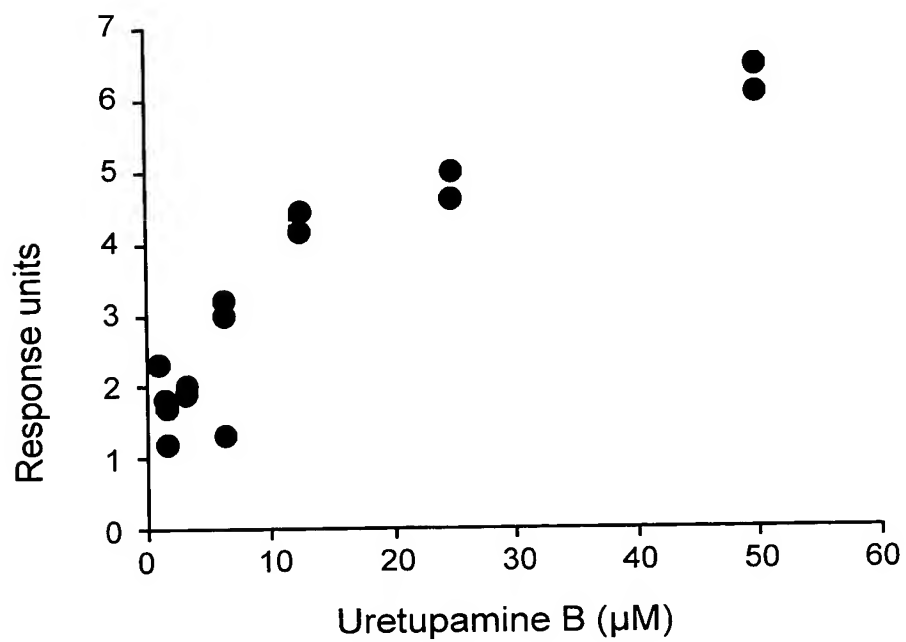
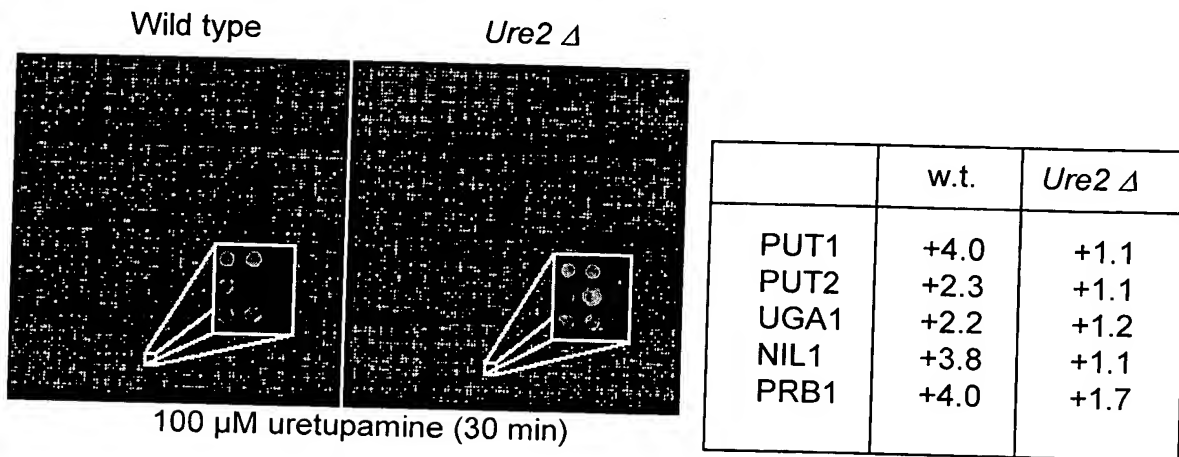
FIG. 24D

FIG. 25A**FIG. 25B**

Gene sets	w.t.	<i>gln3</i> Δ	<i>nil1</i> Δ	<i>ure2</i> Δ
GAP1, MEP2, DAL5, BAT2, AGP1	+1.1	+1.1	-1.0	-1.0
PUT1, PUT2, UGA1, NIL1, PRB1	+2.3	+2.5	+1.6	+1.2

FIG. 25C

Gene sets	w.t.	<i>gln3</i> Δ	<i>nil1</i> Δ	<i>ure2</i> Δ
Whole genome	100%	89%	56%	52%
URE2-dependent genes	100%	115%	51%	59%

FIG. 26A

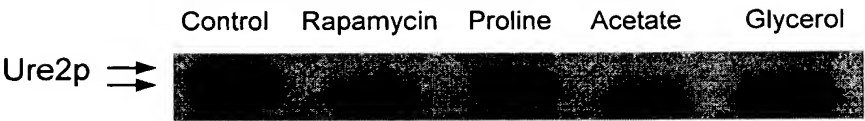


FIG. 26B

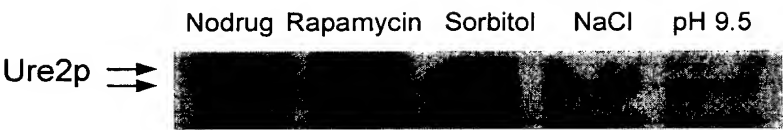


FIG. 26C

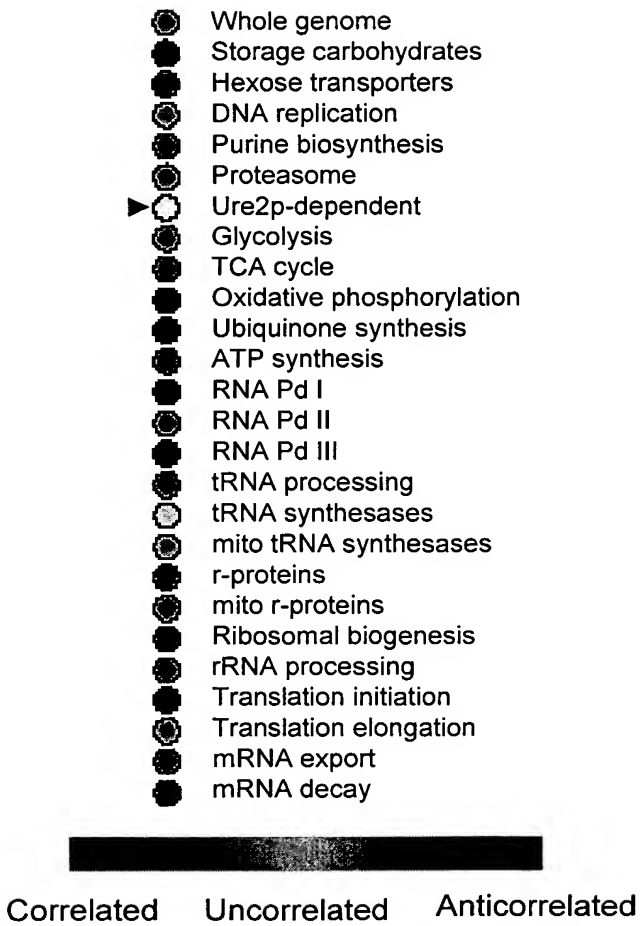


FIG. 26D

	Ethanol	Acetate
PUT1	+11.5	> +10.0
PUT2	+2.8	+1.6
UGA1	+4.7	+3.3
NIL1	+2.6	+2.5
PRB1	+2.3	+1.4
GAP1	+3.3	-9.0
DAL1	+1.7	-4.8
DAL2	+3.1	-1.5
DAL3	+2.1	< -10.0
CAR1	+2.6	-1.4

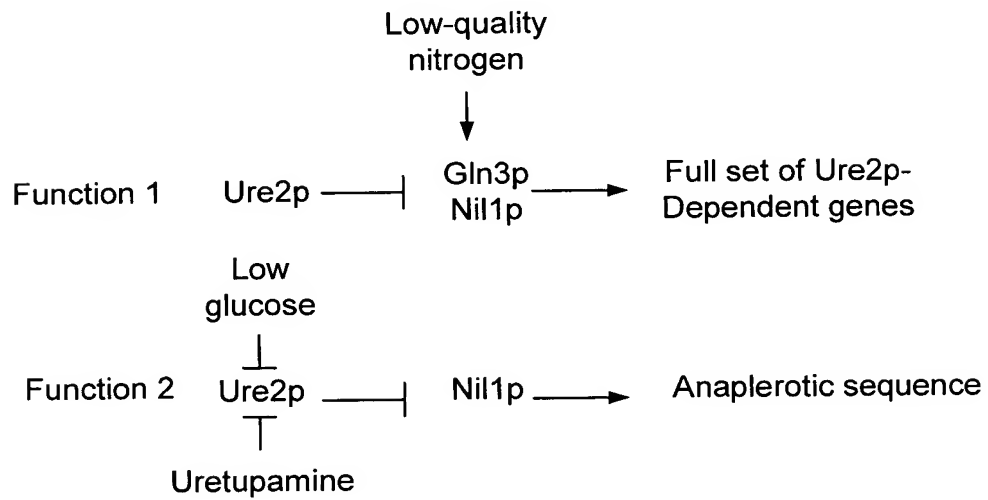
FIG. 26E

FIG. 27A

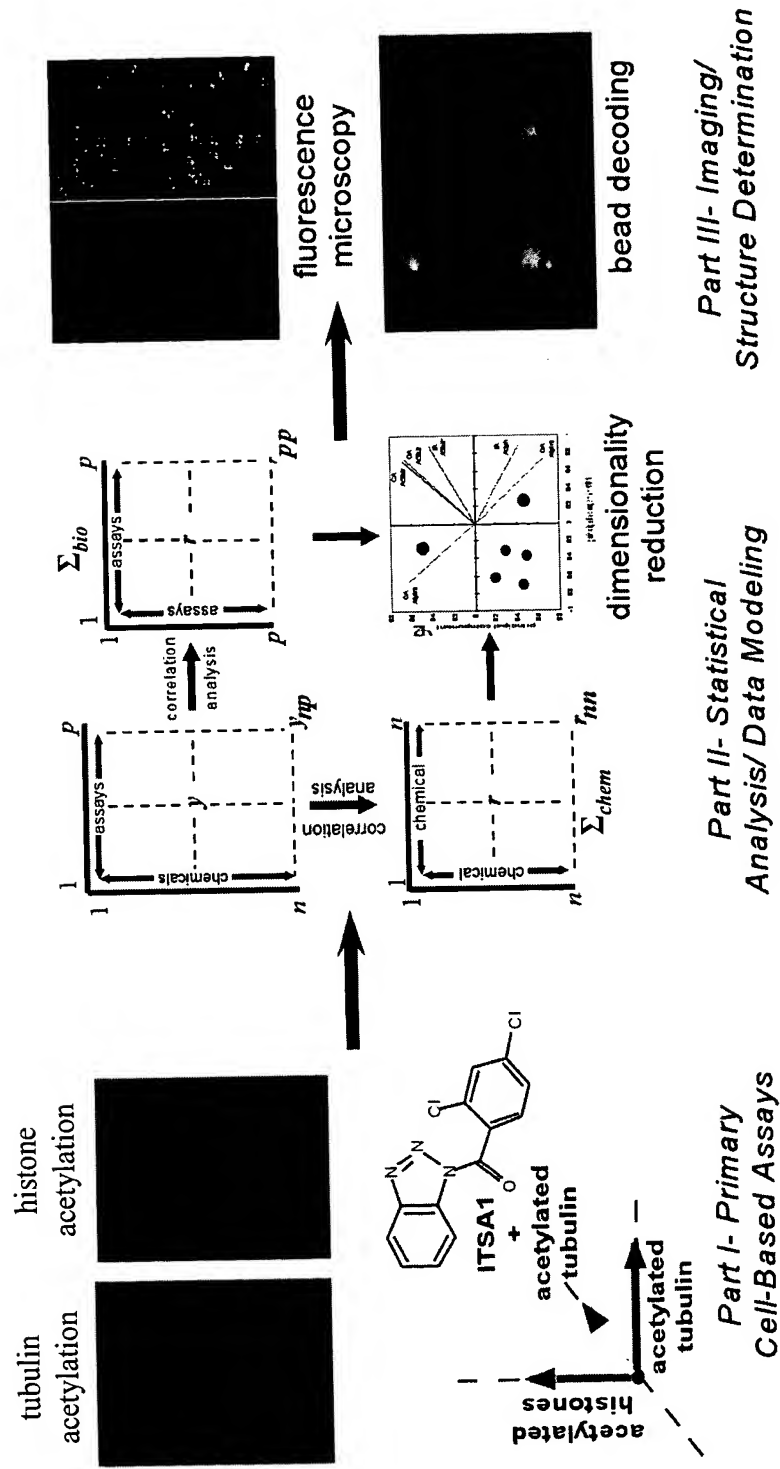
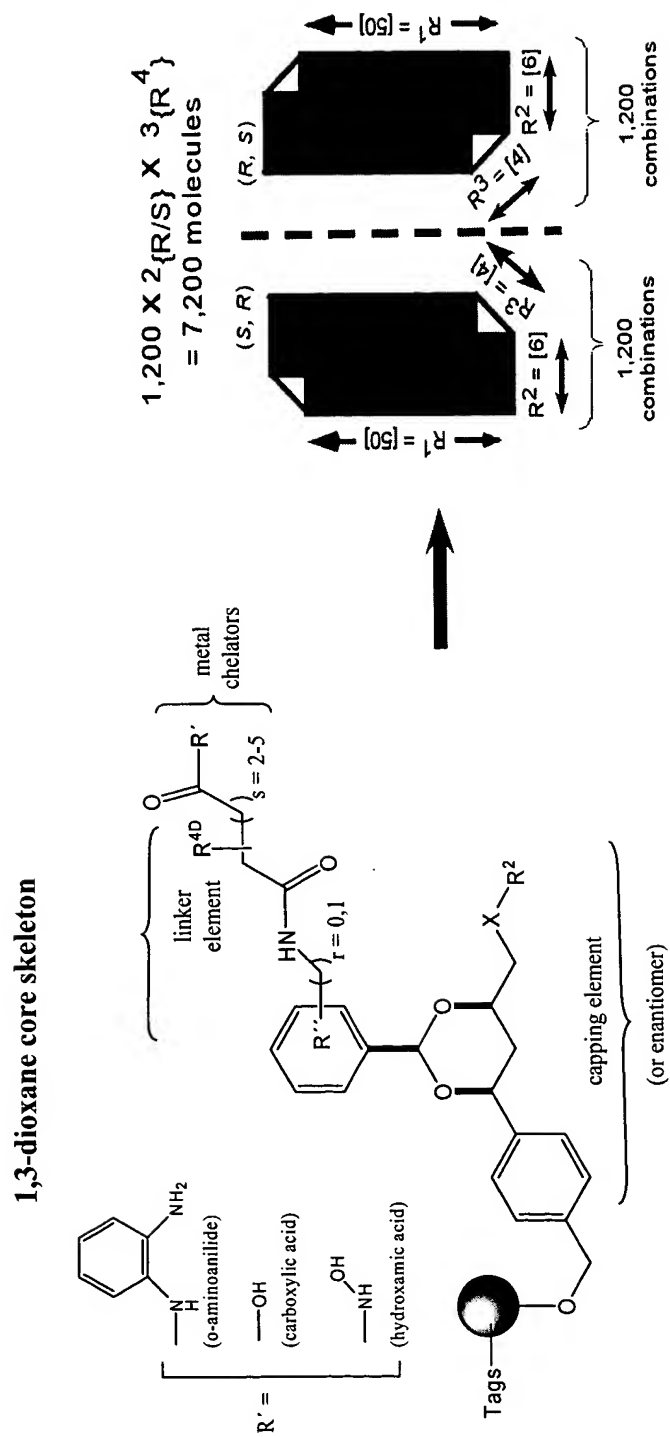


FIG. 27B



Biasing elements in diversity-oriented synthesis

FIG. 27C

	Assay	Abbreviation	Compounds screened in duplicate
1.	Acetylated tubulin	AcTubulin	7,392
2.	Acetylated tubulin + ITSA1 (chemical genetic modifier)	ITSA1+AcTubulin	2,464 hydroxamic acids
3.	Acetylated lysine	AcLysine	7,392
4.	Acetylated histone H3	AcHistH3	2,464 hydroxamic acids
5.	Acetylated histone H4	AcHistH4	2,464 hydroxamic acids

Table 1. Summary of chemical genetic screens

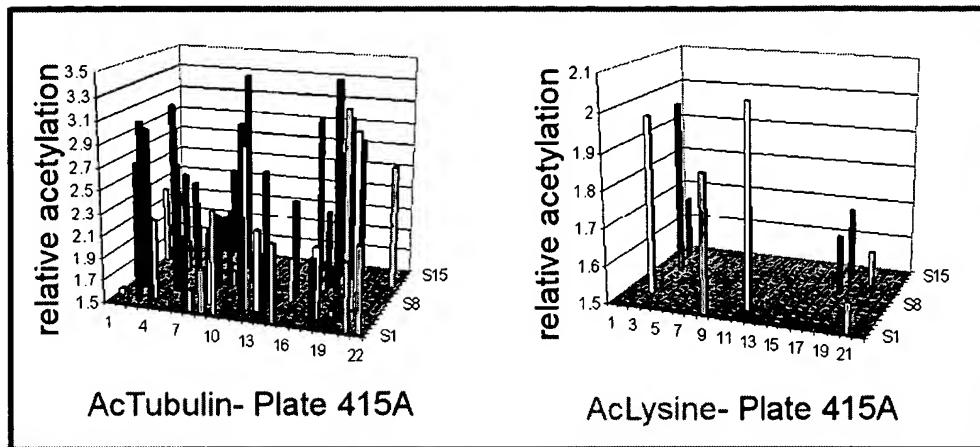
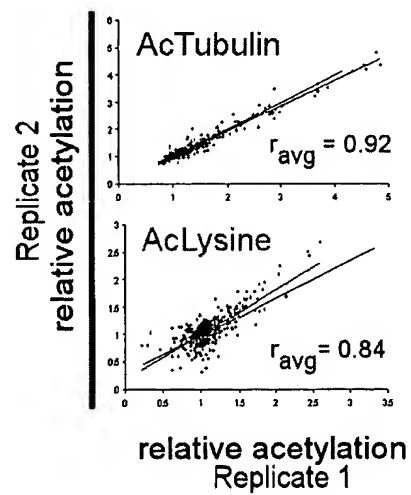
FIG. 28A**FIG. 28B**

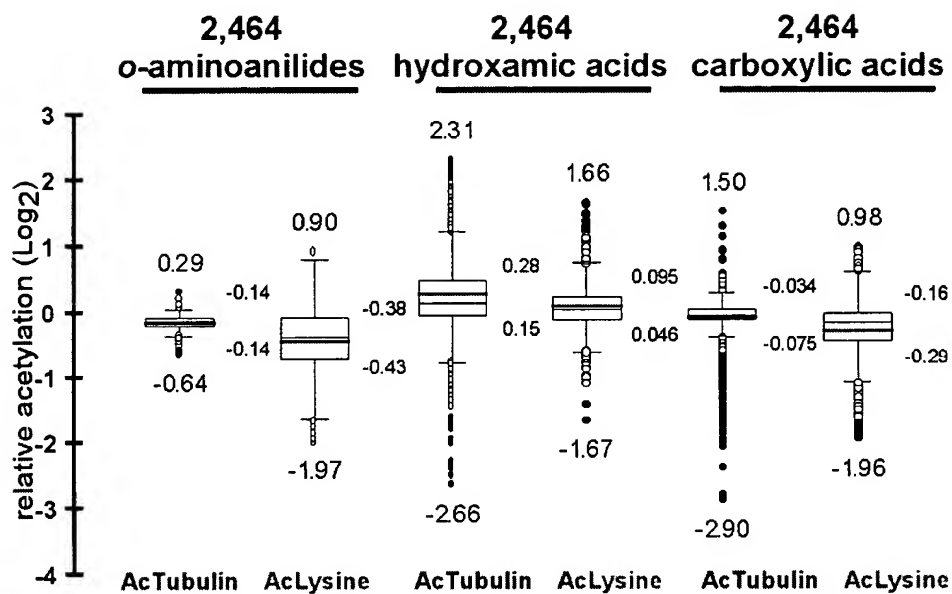
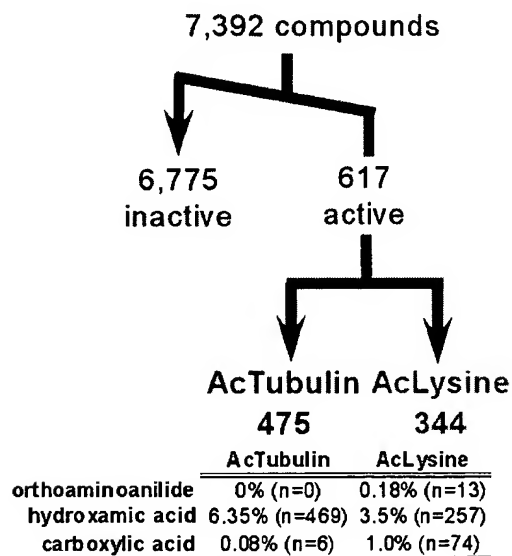
FIG. 28C**FIG. 28D**

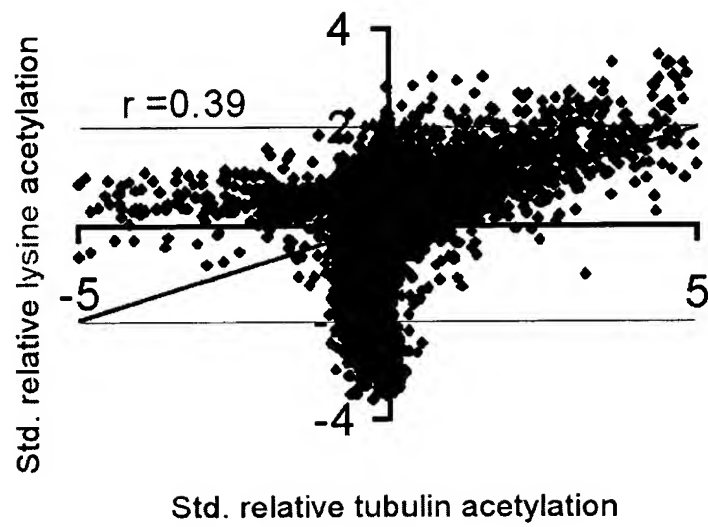
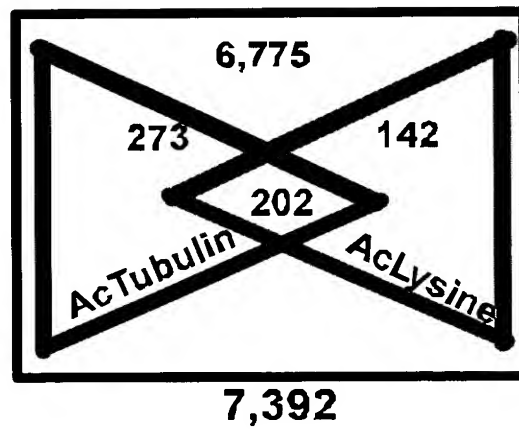
FIG. 29A**FIG. 29B**

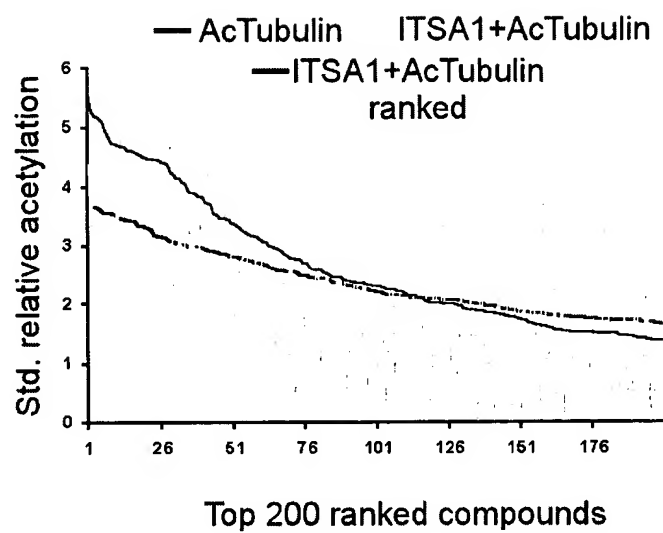
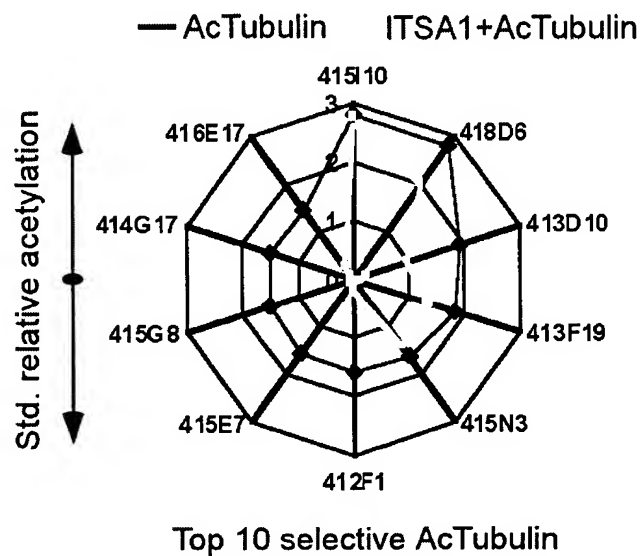
FIG. 29C**FIG. 29D**

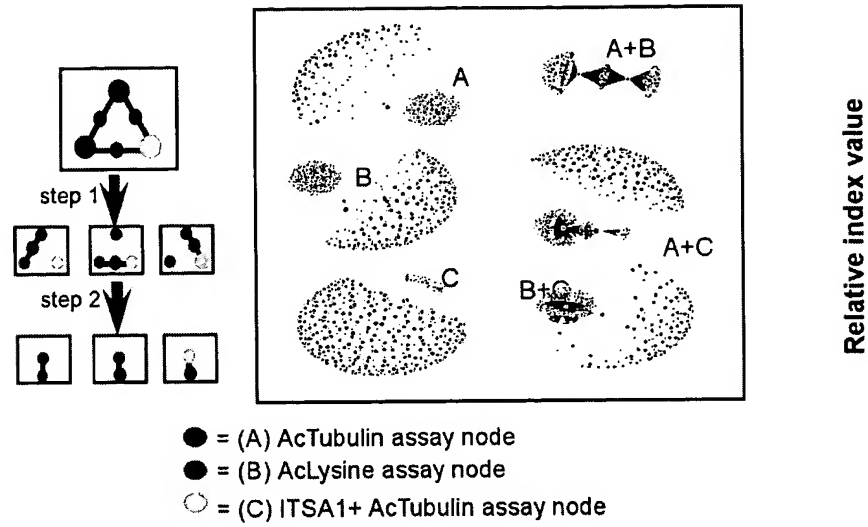
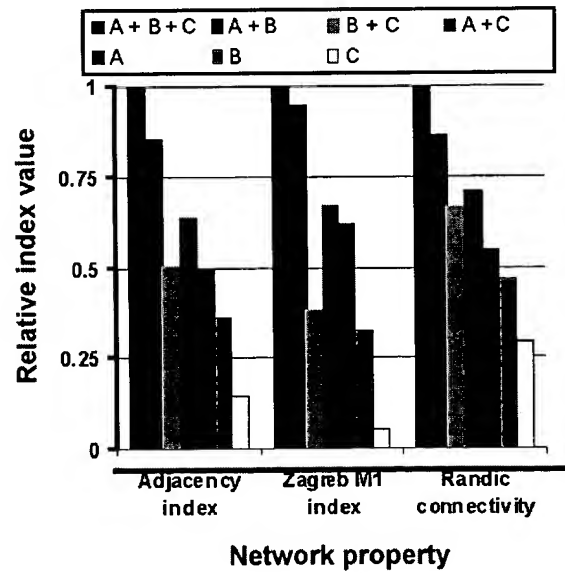
FIG. 30B**FIG. 30C**

FIG. 31

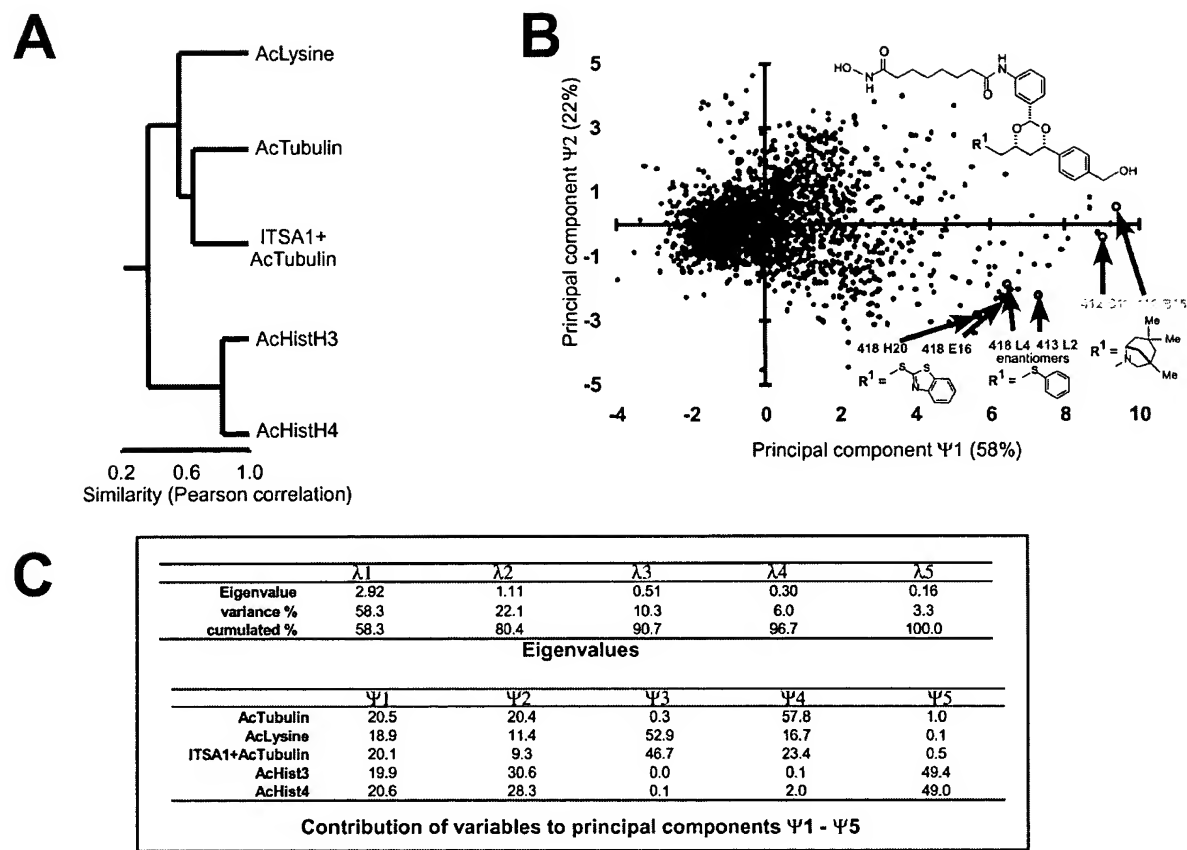


FIG. 32

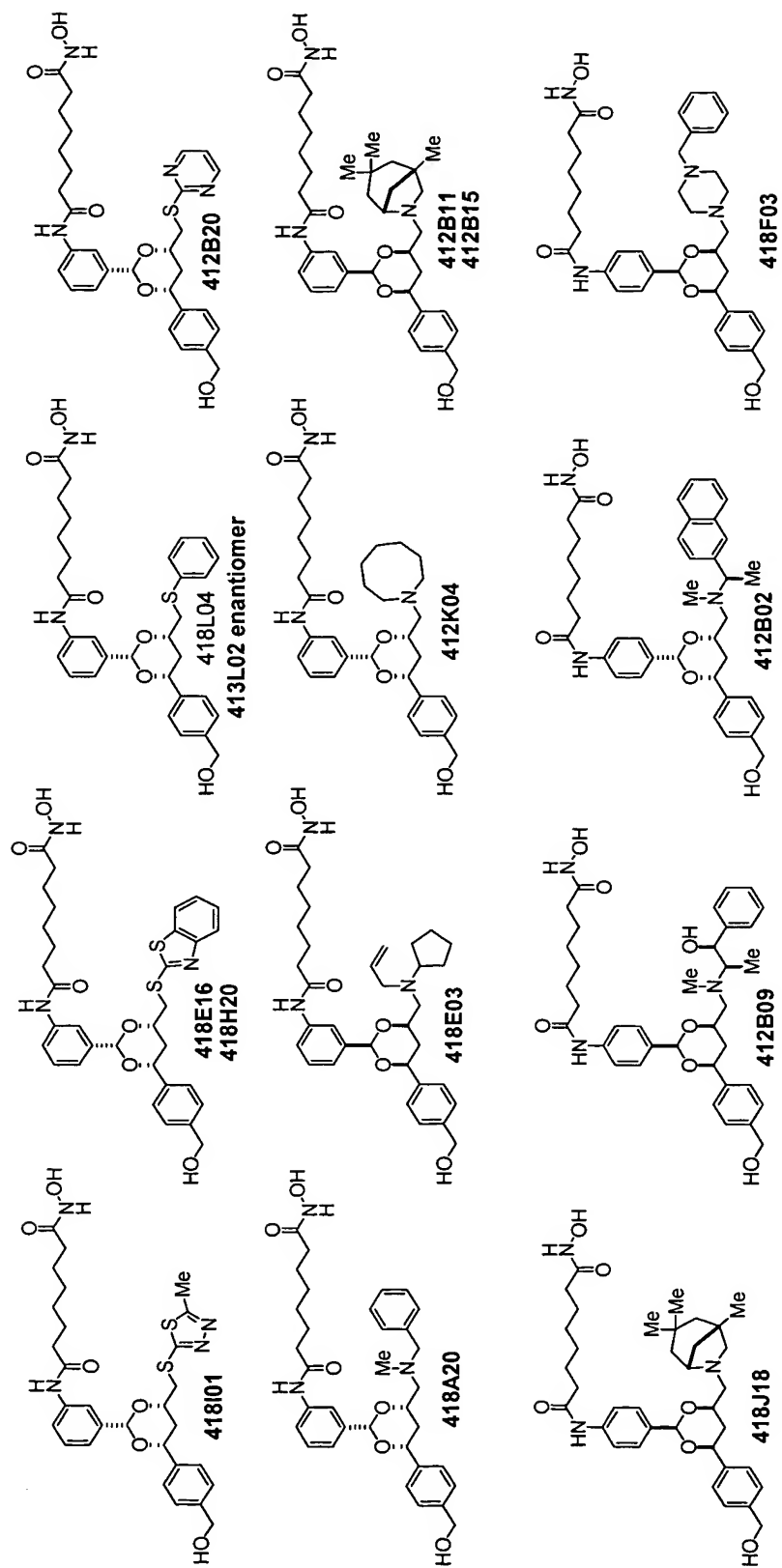


FIG. 33A

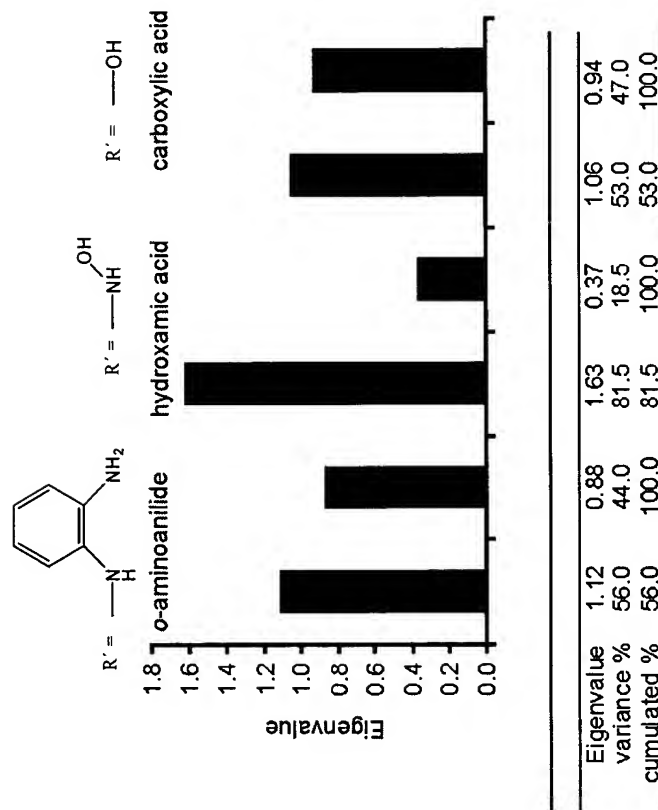


FIG. 33B

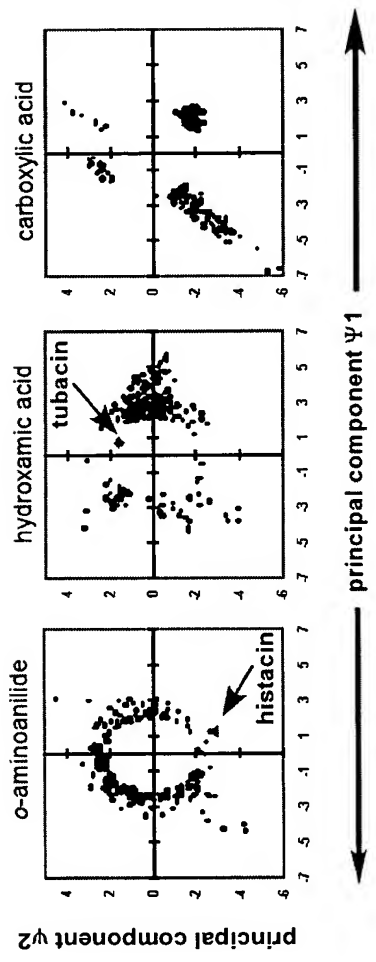


FIG. 33C

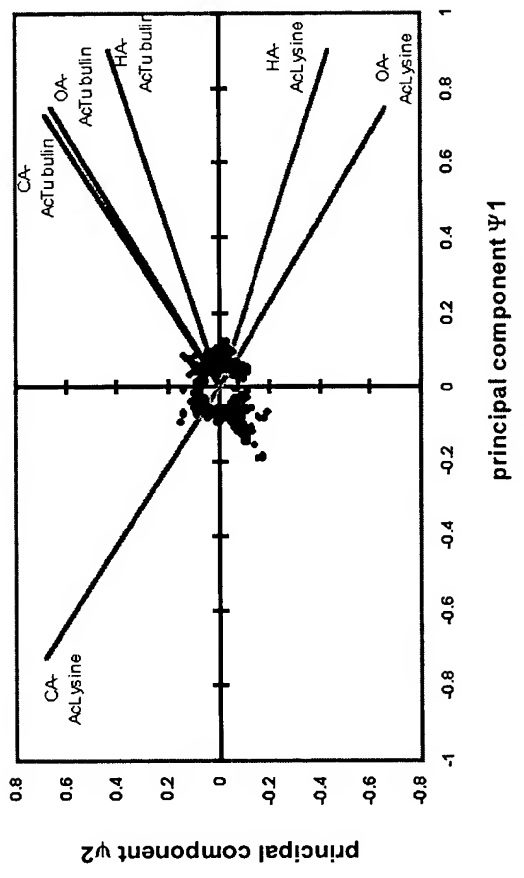


FIG. 34A

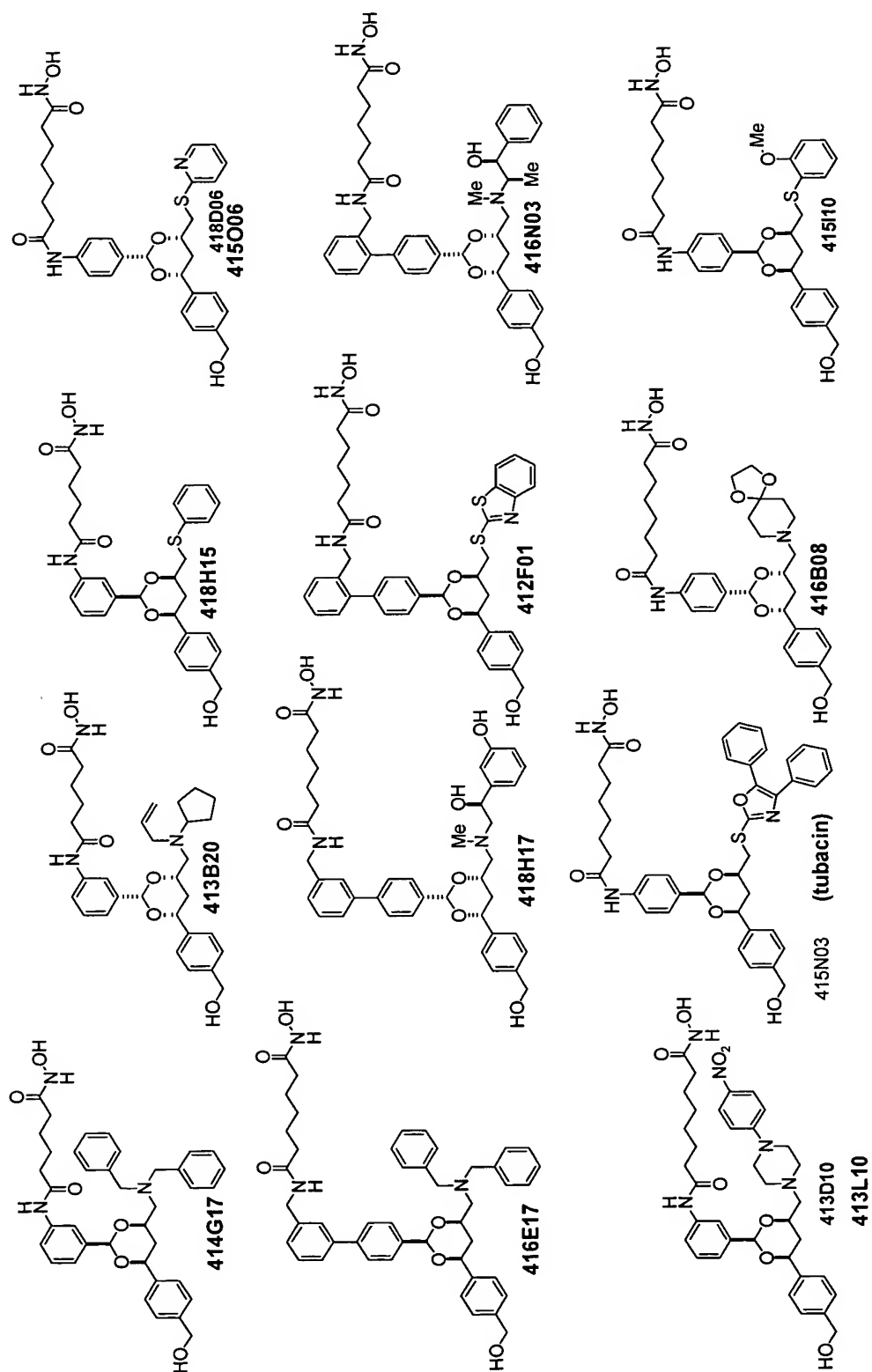


FIG. 34B

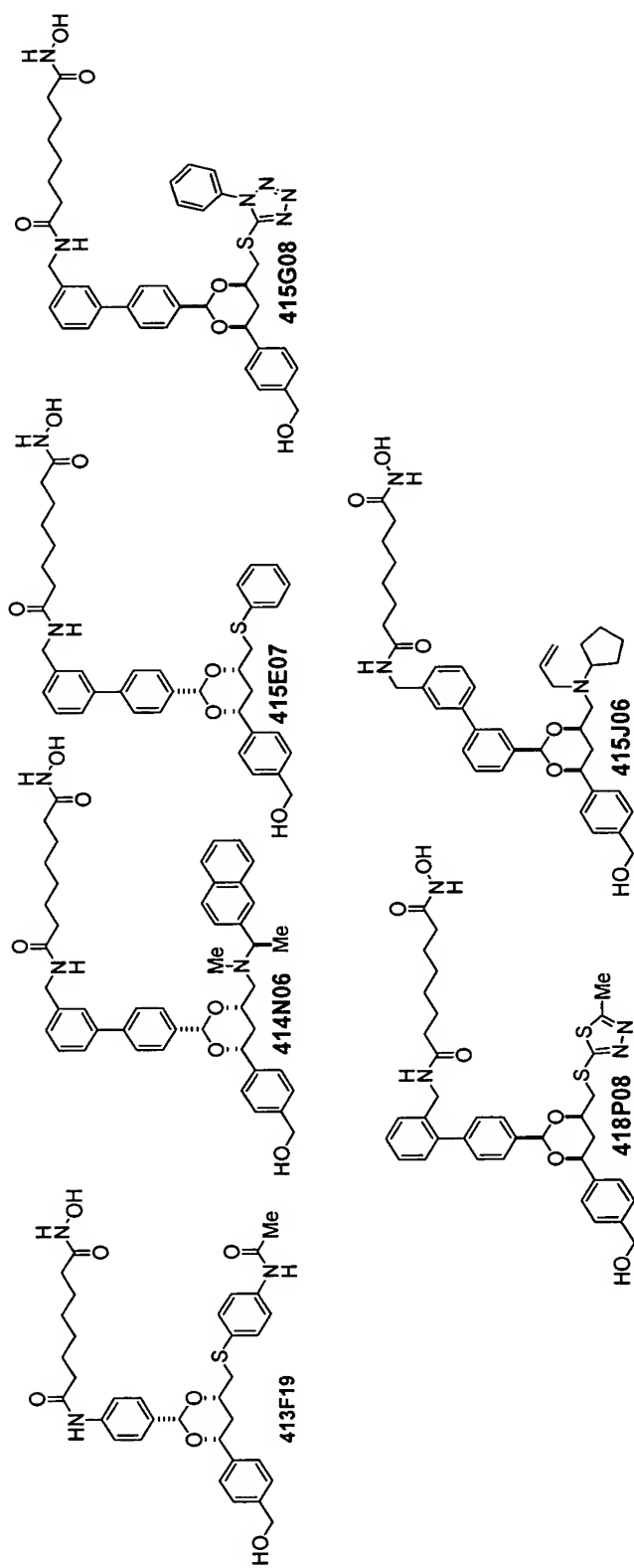


FIG. 35A

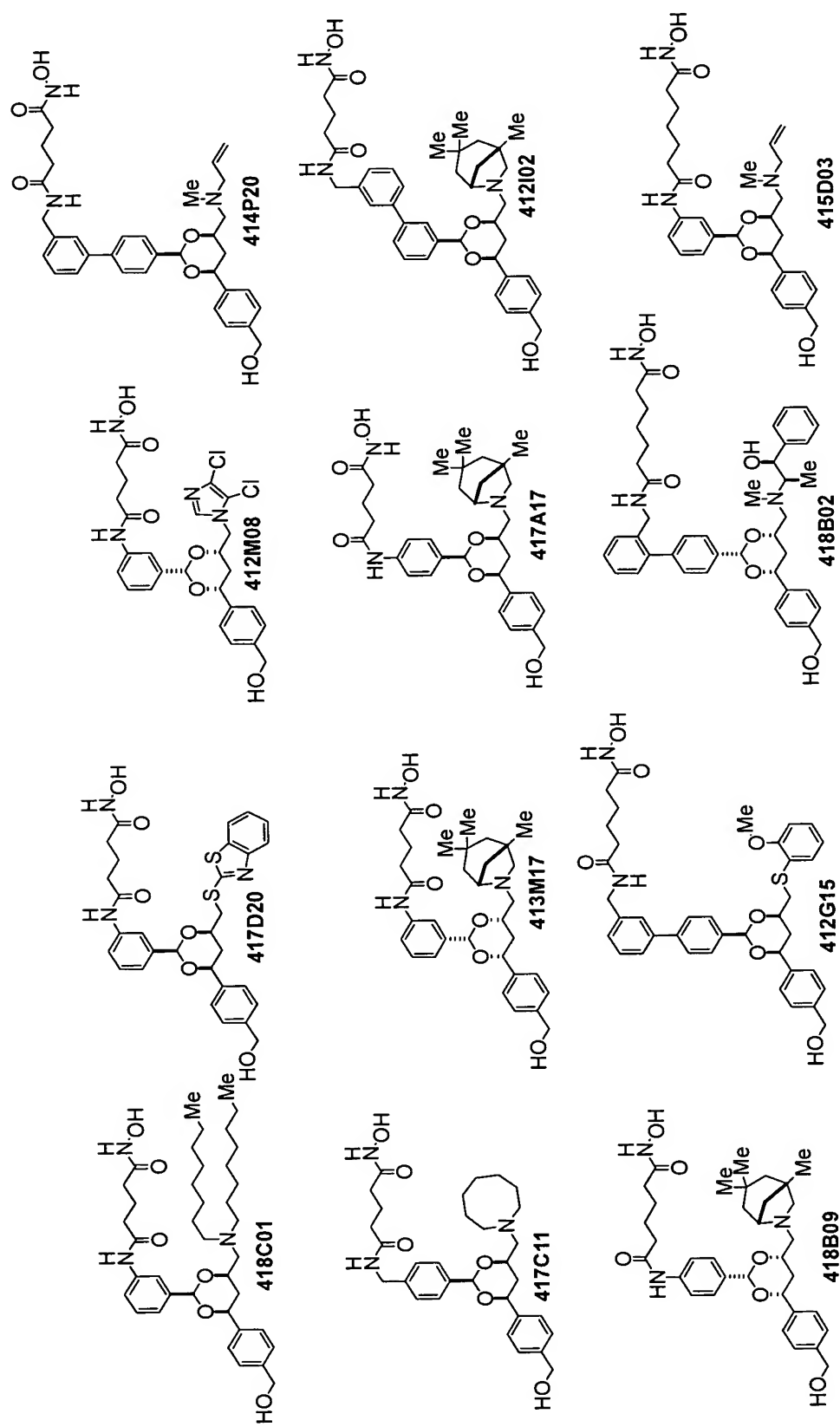


FIG. 35B

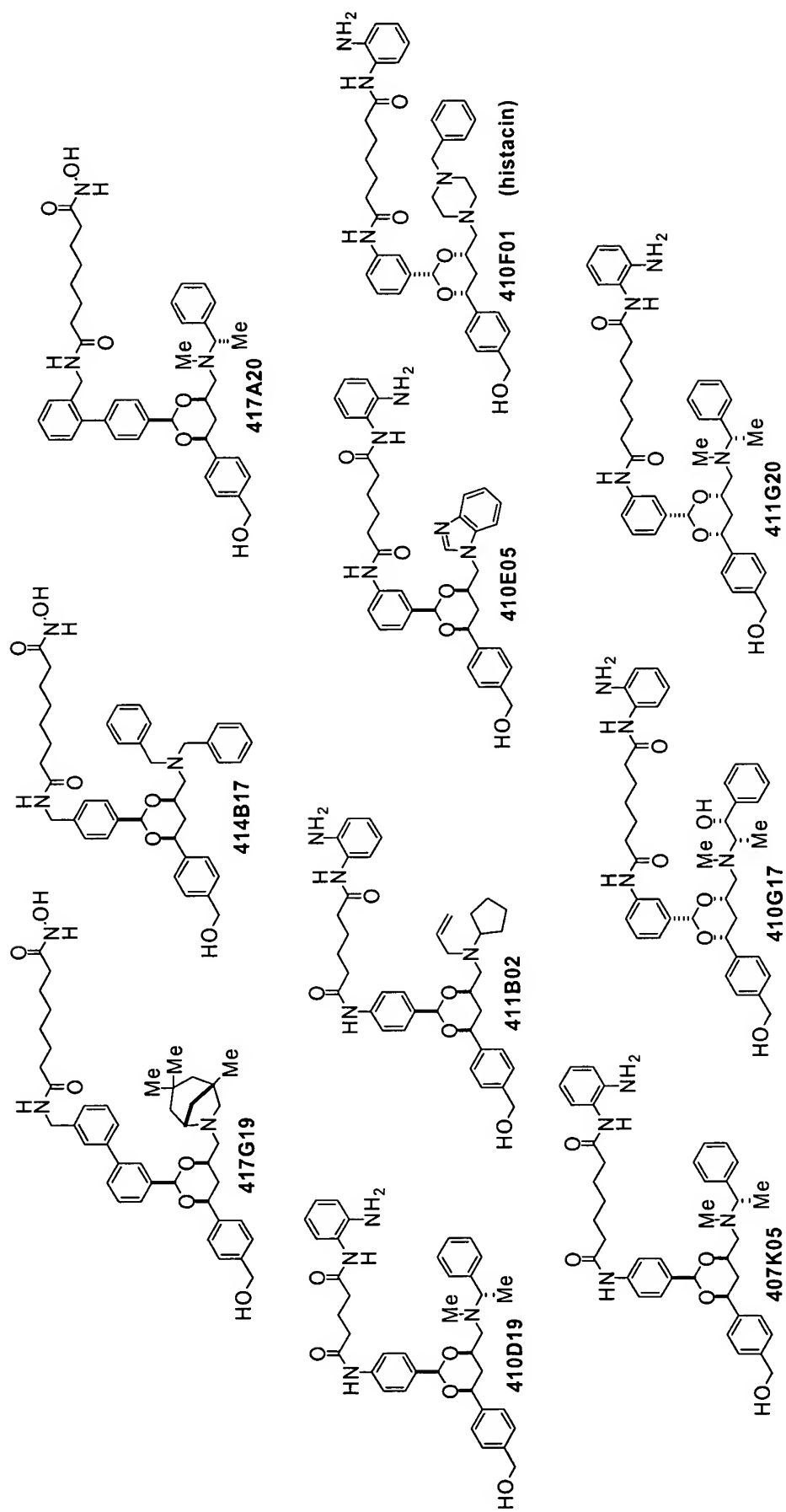


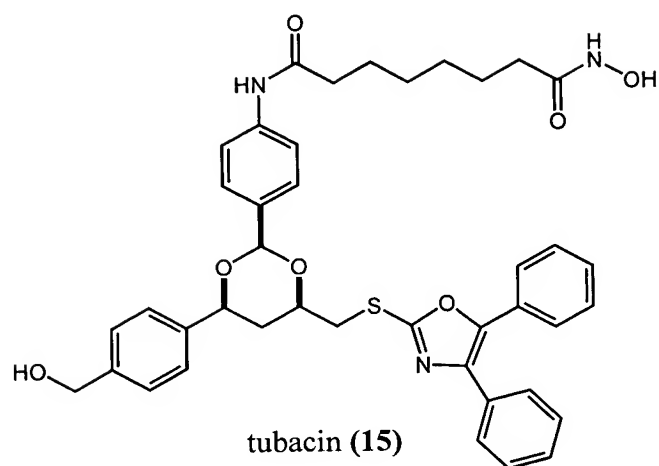
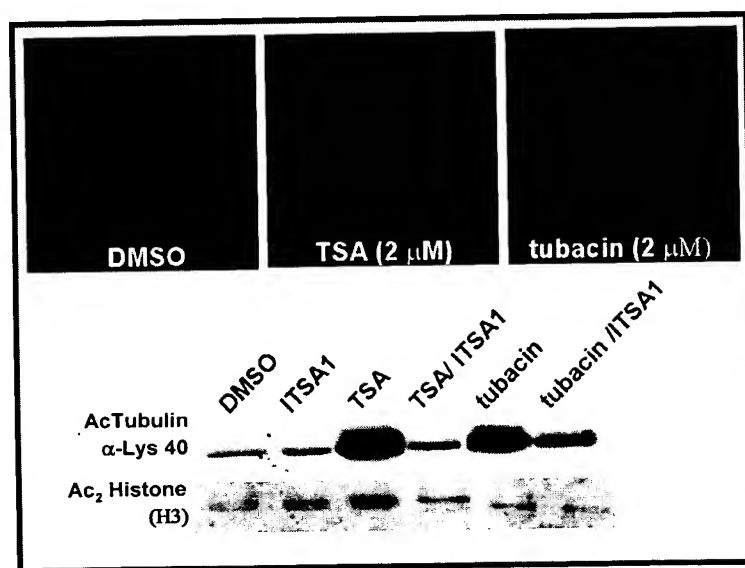
FIG. 36A**FIG. 36B**

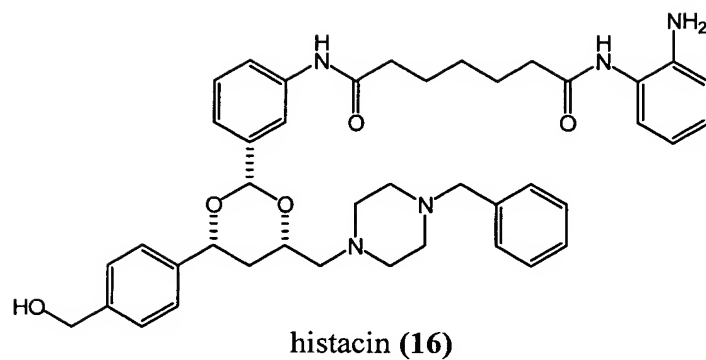
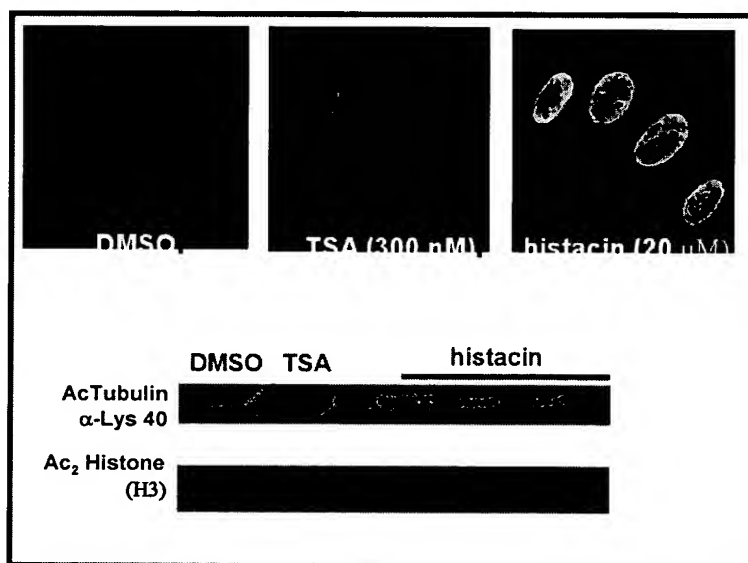
FIG. 36C**FIG. 36D**

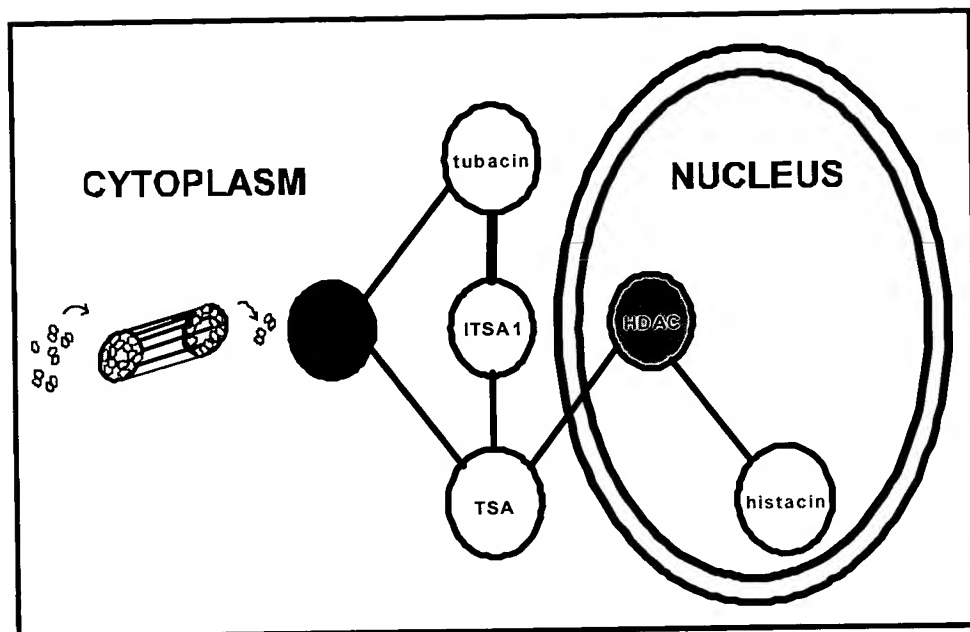
FIG. 36E

FIG. 37A

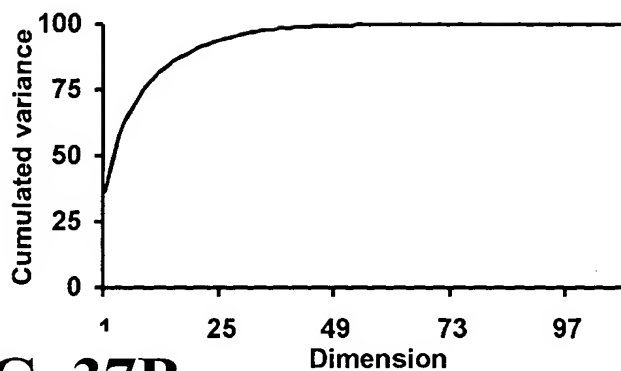


FIG. 37B

	F1	F2	F3	F4	F5
Eigenvalue	40.5	9.7	8.6	6.5	5.2
variance %	36.1	8.6	7.7	5.8	4.6
cumulated %	36.1	44.8	52.5	58.3	62.9

FIG. 37C

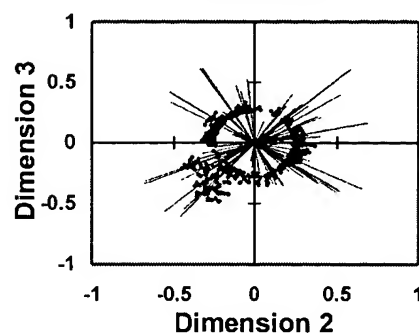
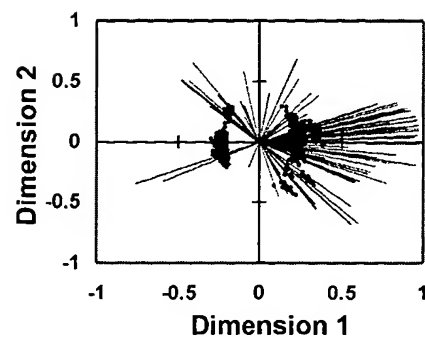


FIG. 37D

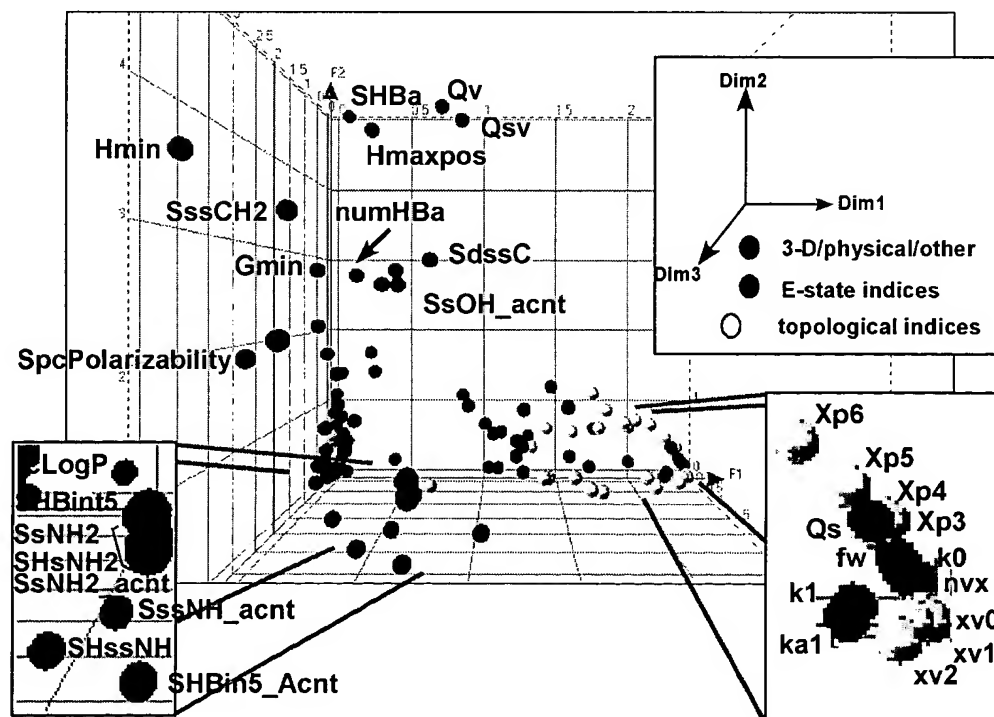


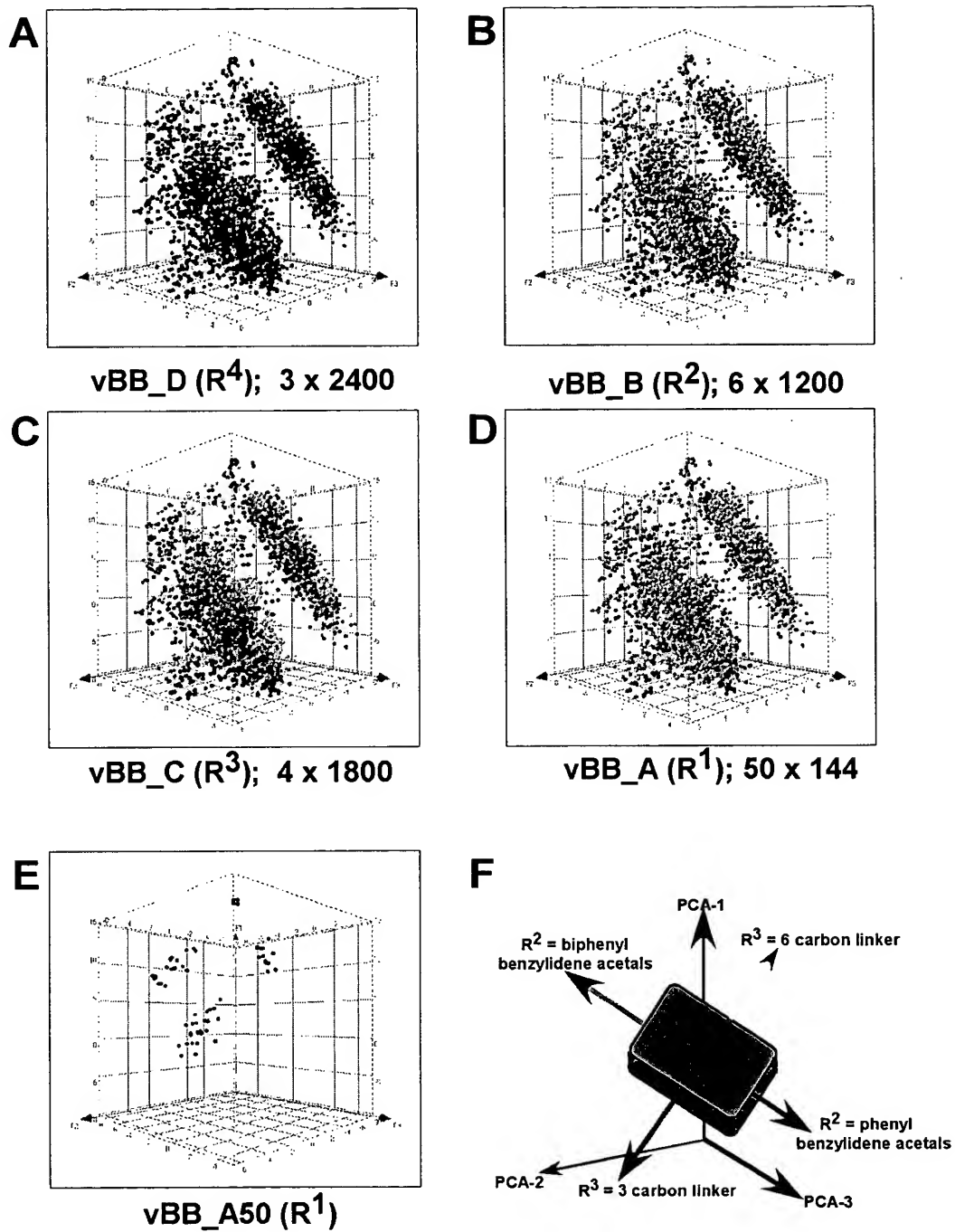
FIG. 38

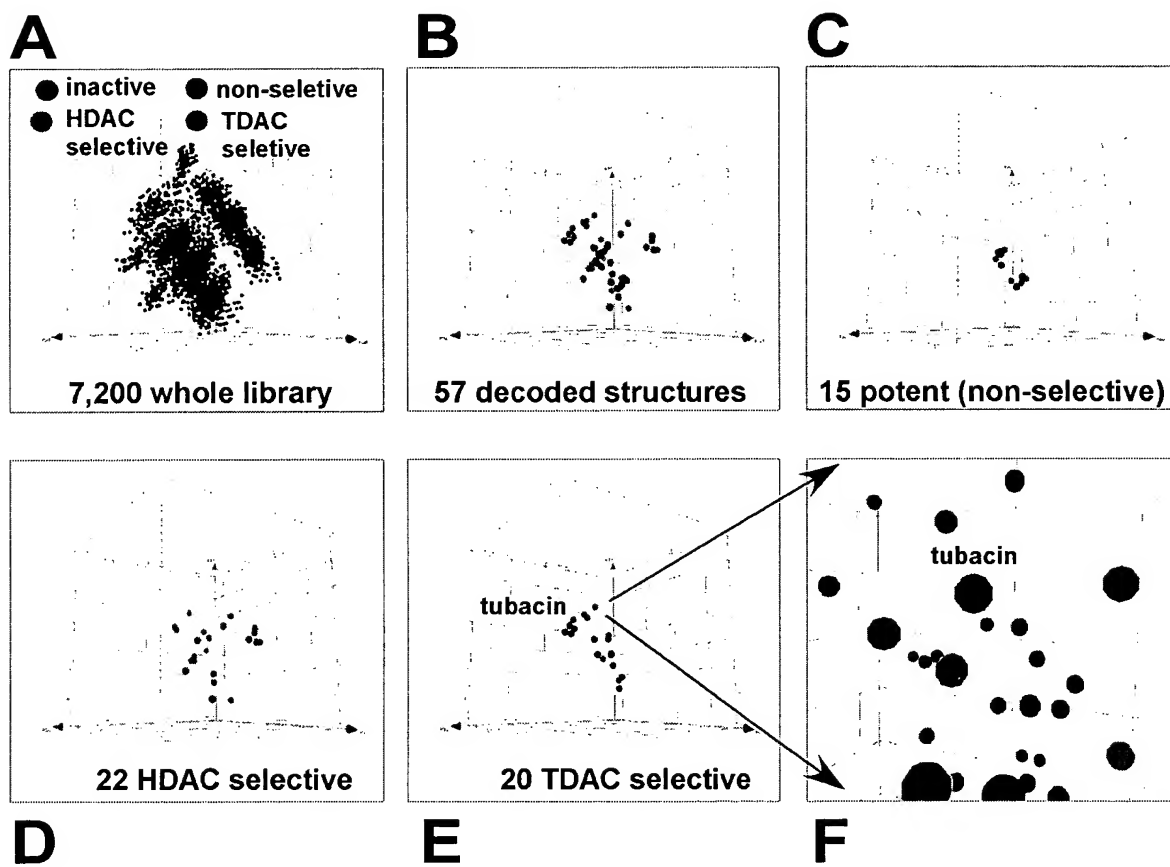
FIG. 39

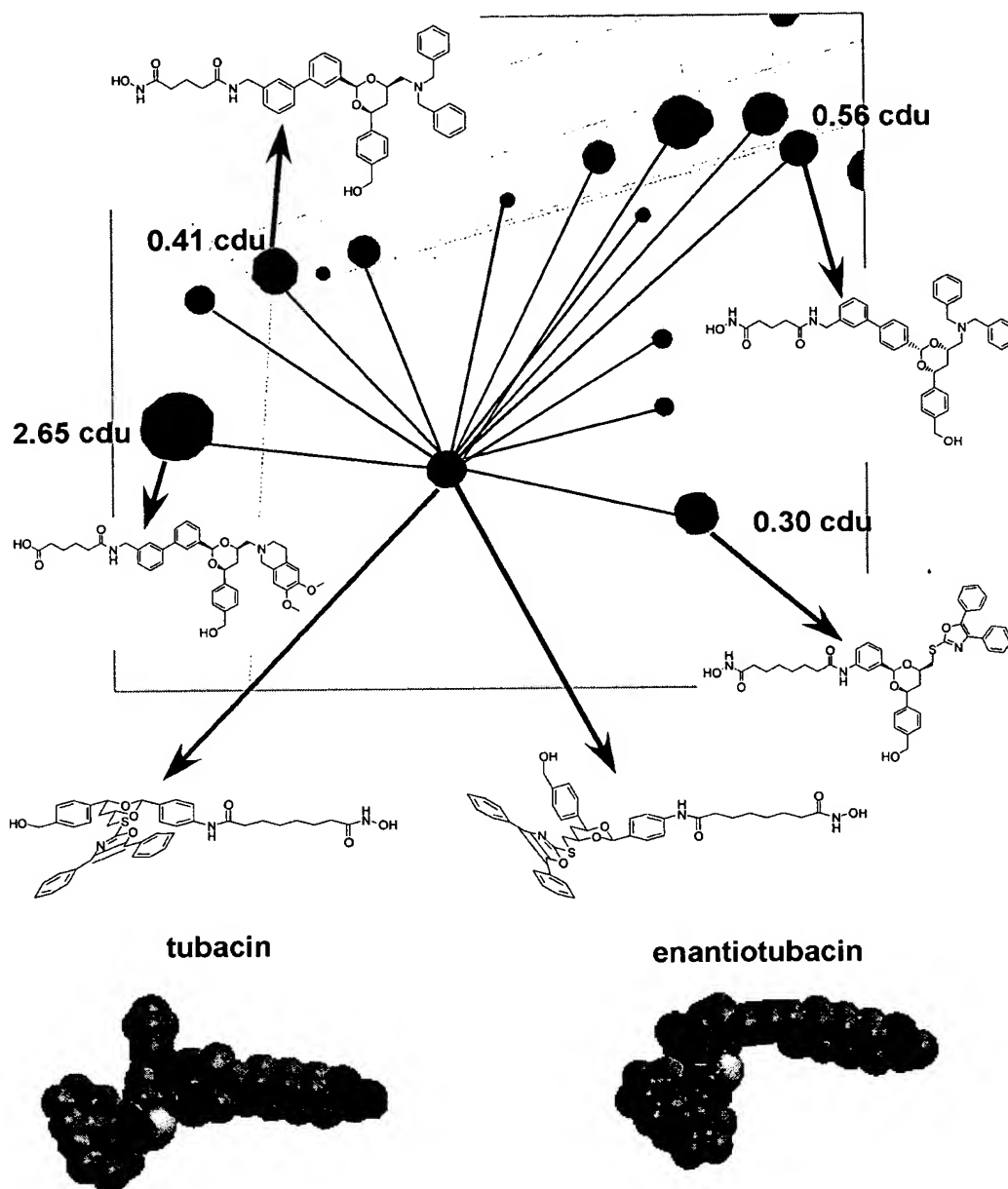
FIG. 40

FIG. 41A

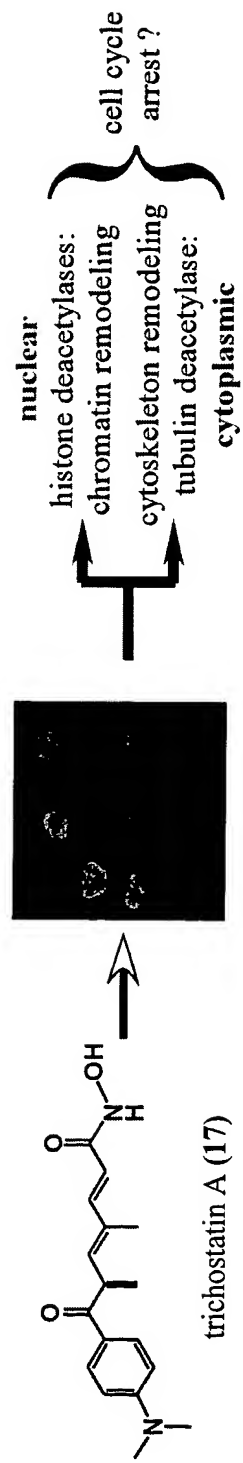


FIG. 41B

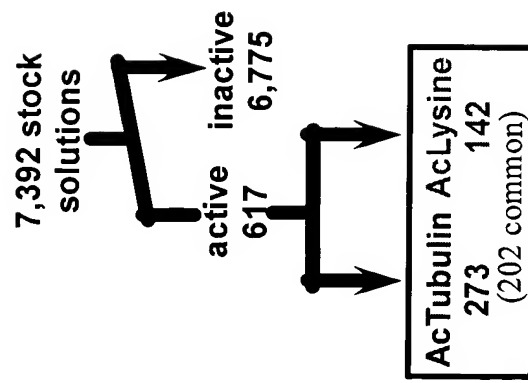


FIG. 41C

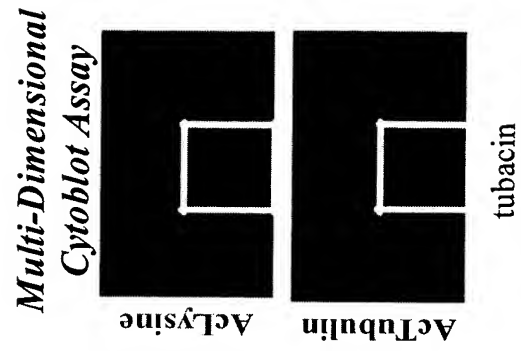
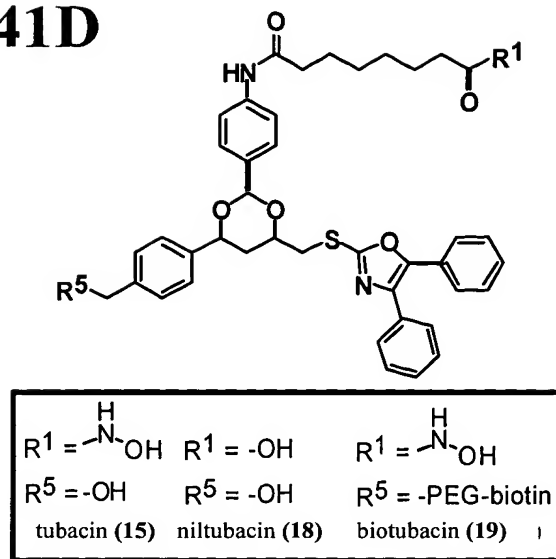
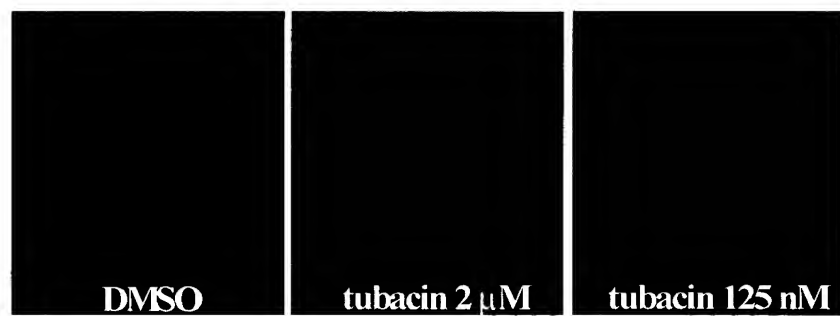


FIG. 41D**FIG. 41E****FIG. 41F**

	DMSO	TSA	tubacin	niltubacin
AcTubulin (α -Lys40)				
Ac ₂ Histone (H3)				
α -tubulin				

FIG. 42A

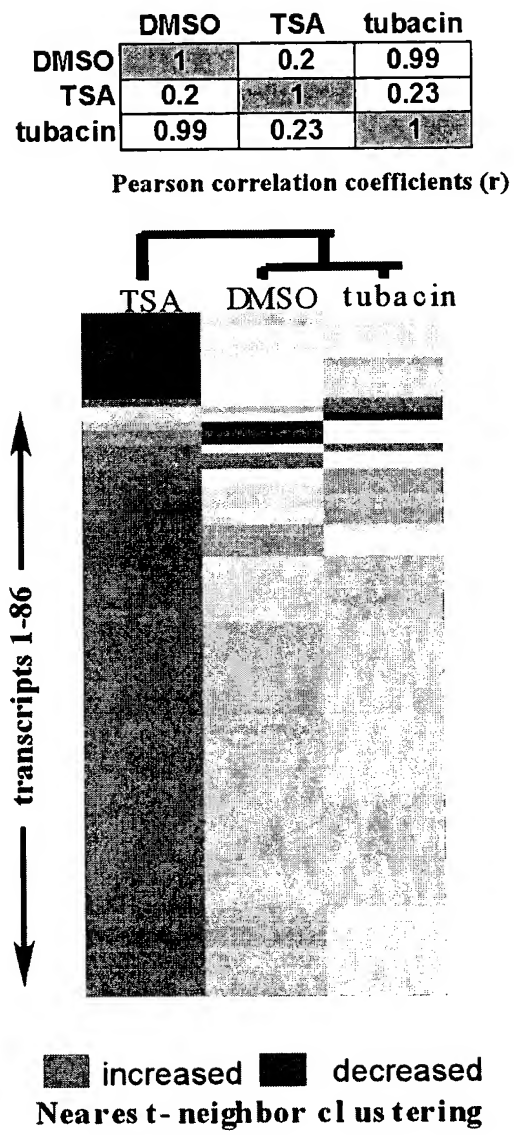


FIG. 42B

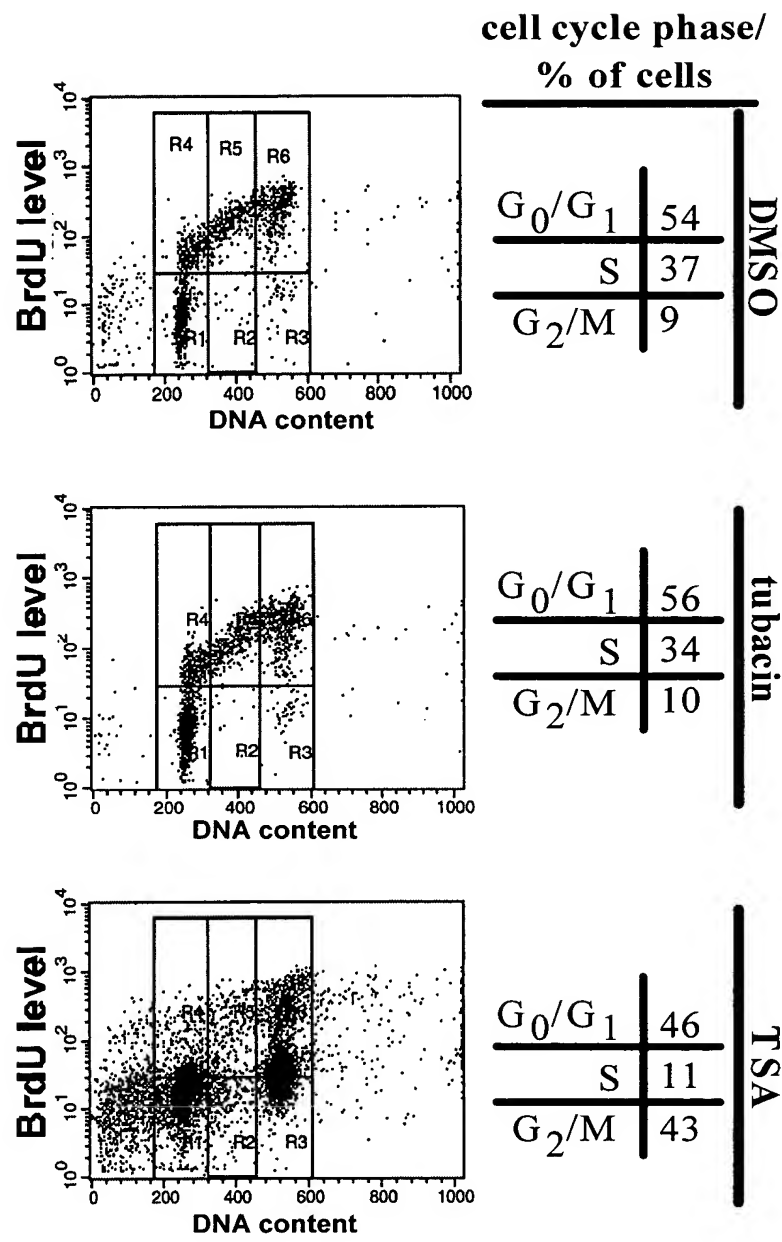


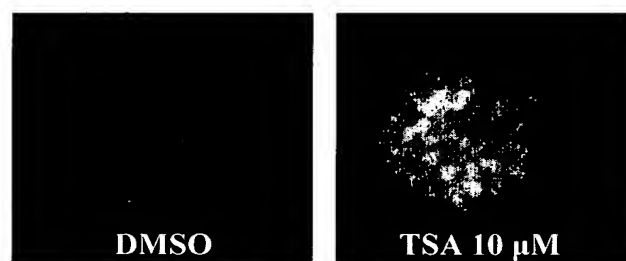
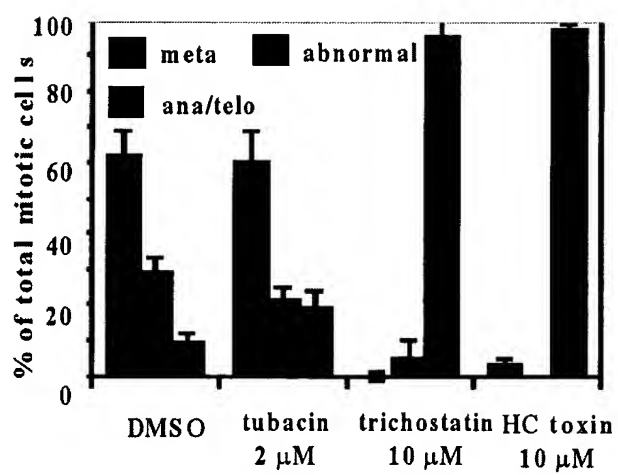
FIG. 42C**FIG. 42D**

FIG. 43B

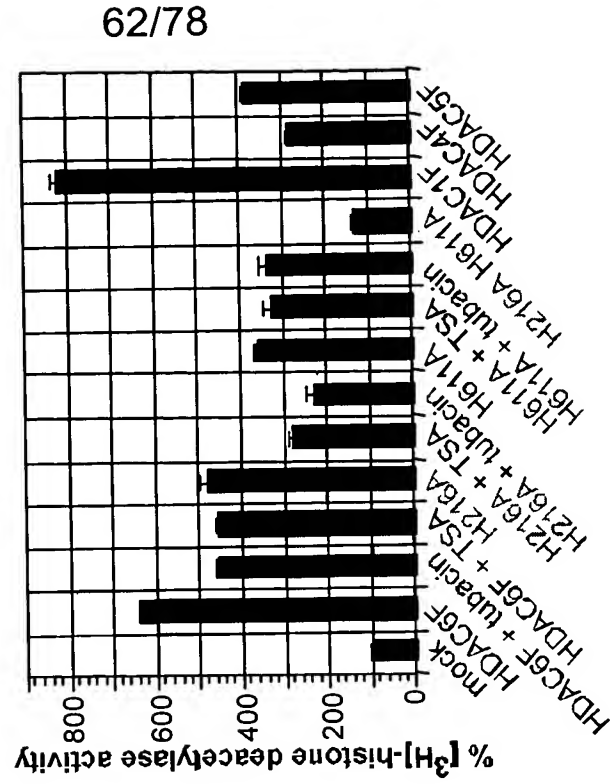
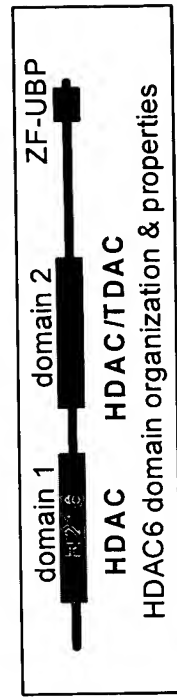


FIG. 43A

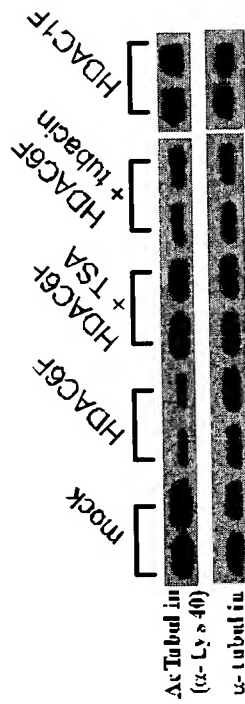


FIG. 43C

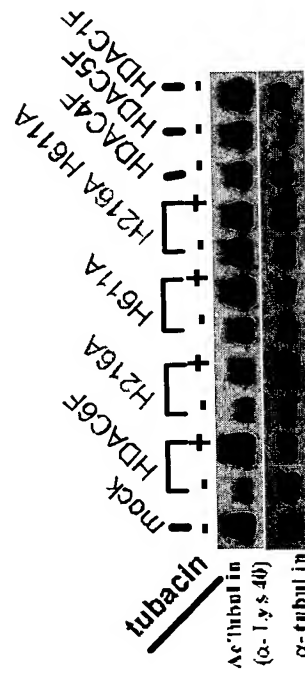


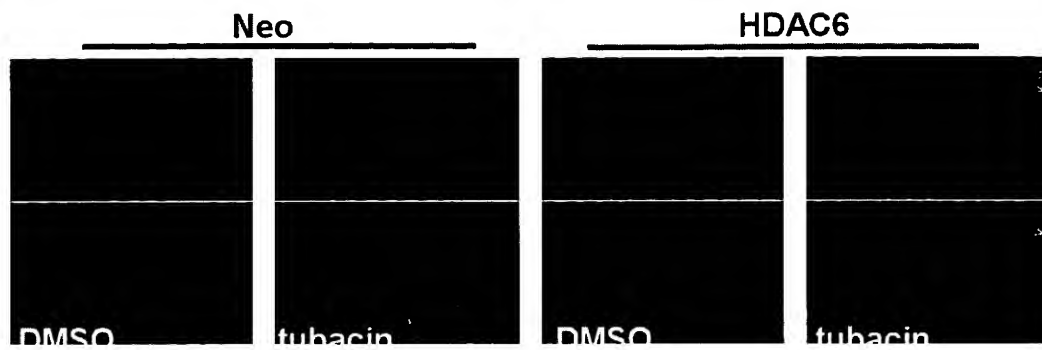
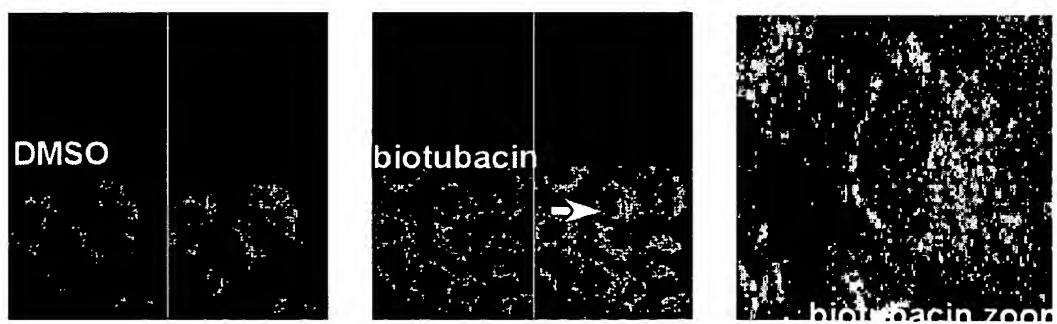
FIG. 43D**FIG. 43E****FIG. 43F**

FIG. 44A

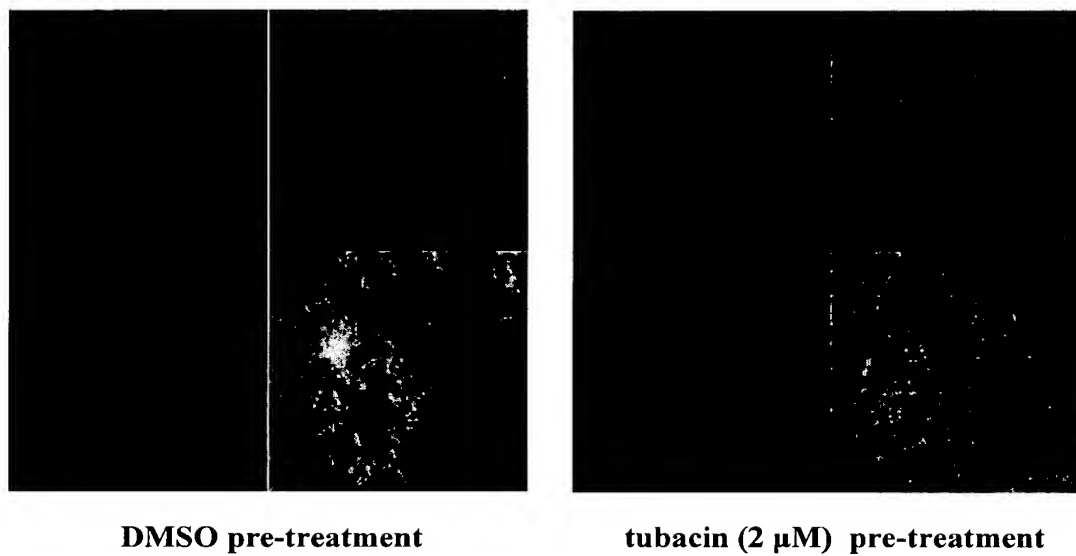


FIG. 44B

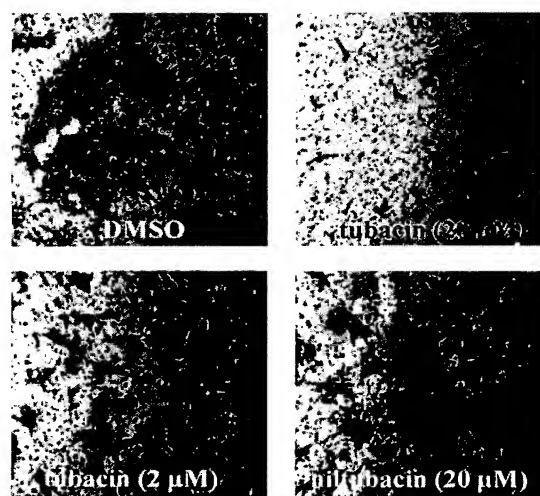


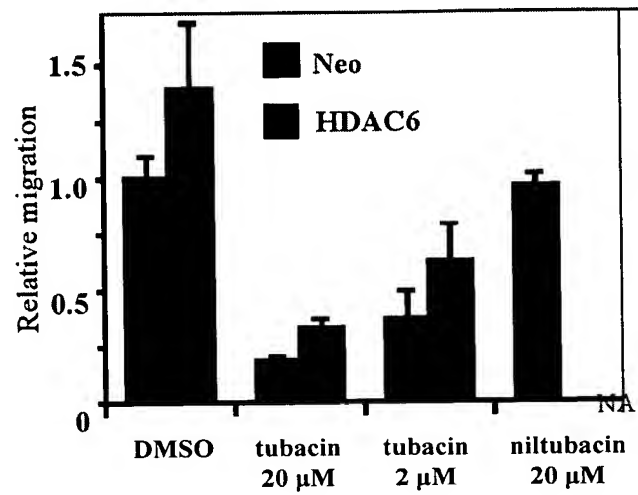
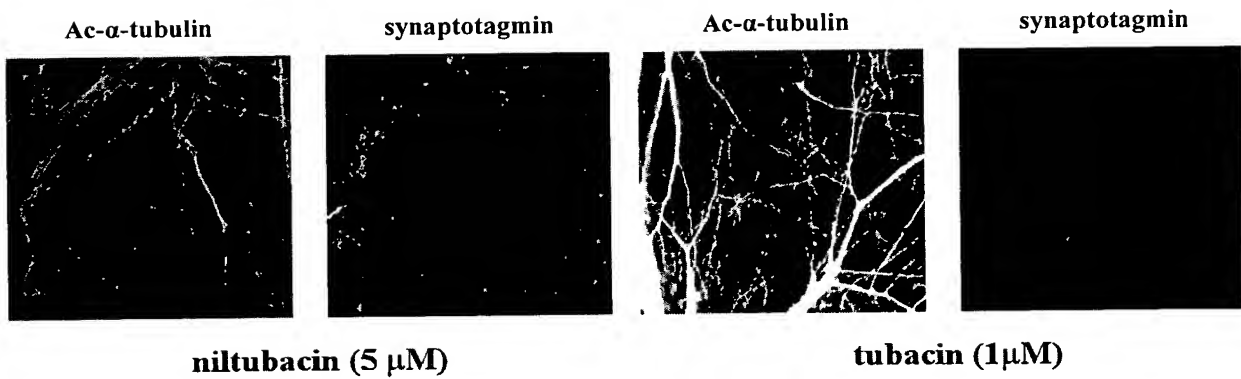
FIG. 44C**FIG. 44D**

FIG. 45A

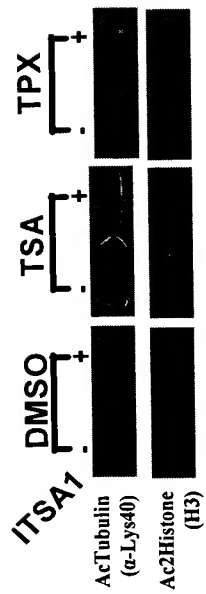
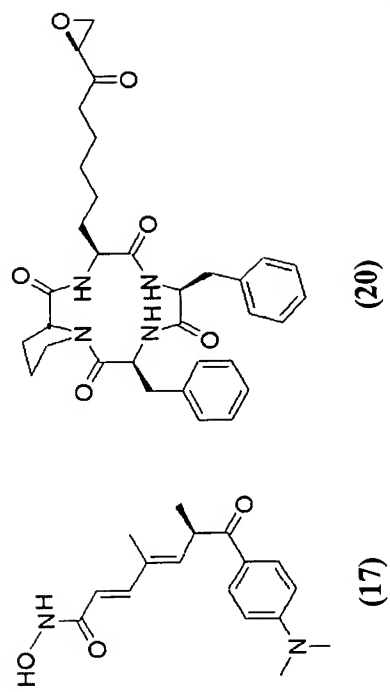


FIG. 45B



66/78

FIG. 45C

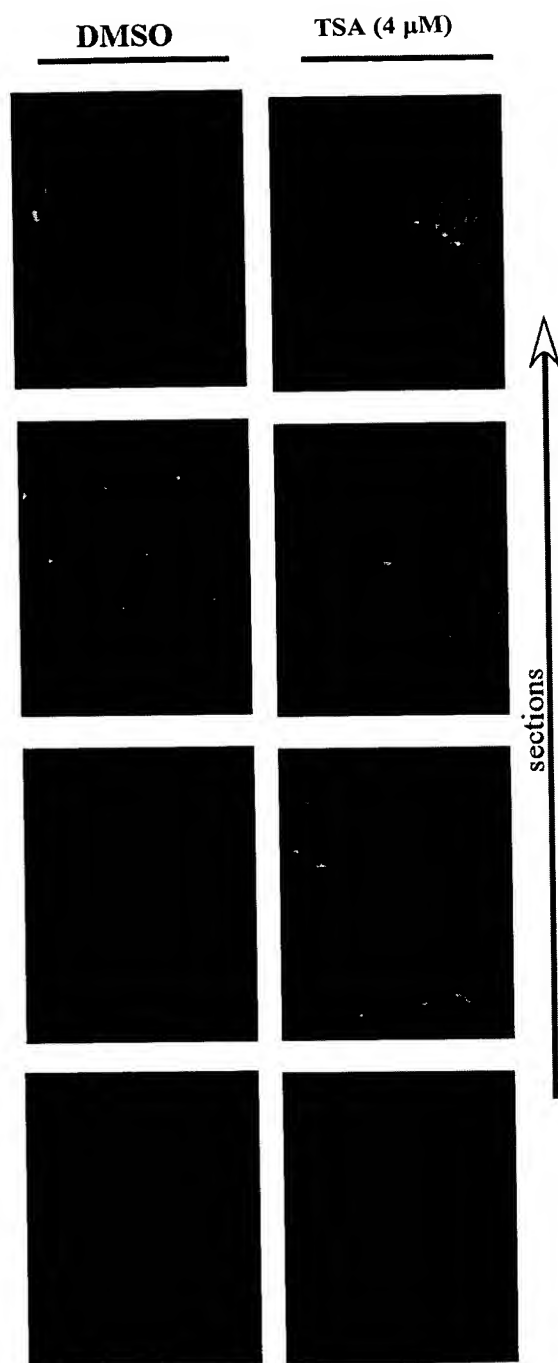
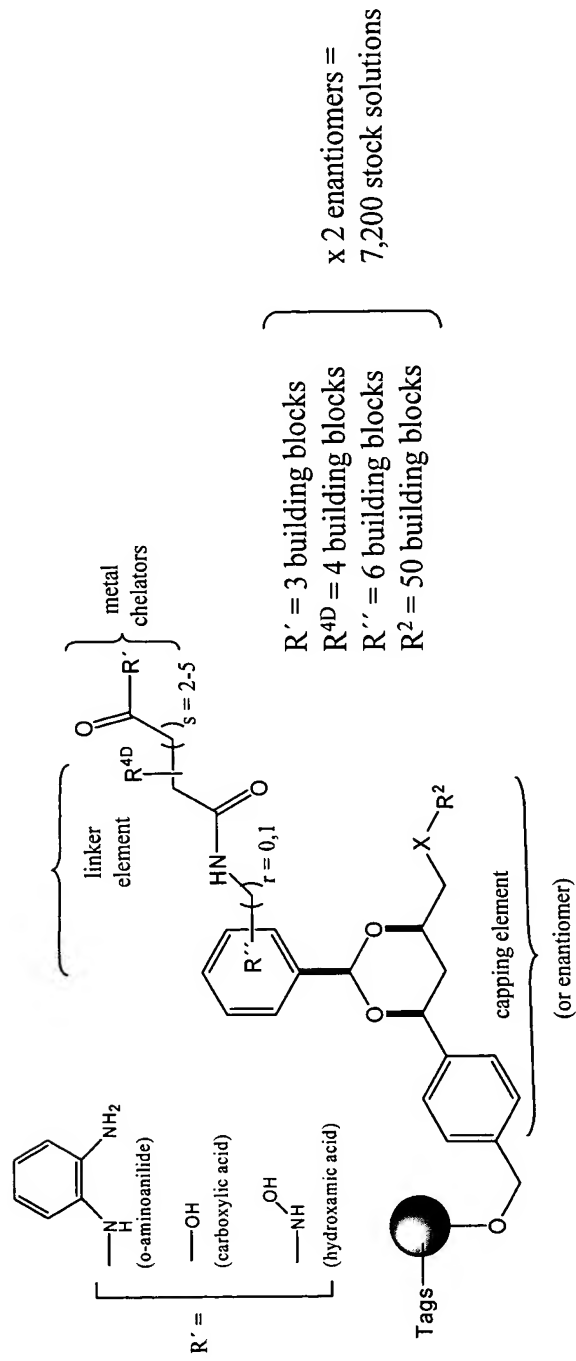


FIG. 45D



Biasing elements in diversity-oriented synthesis

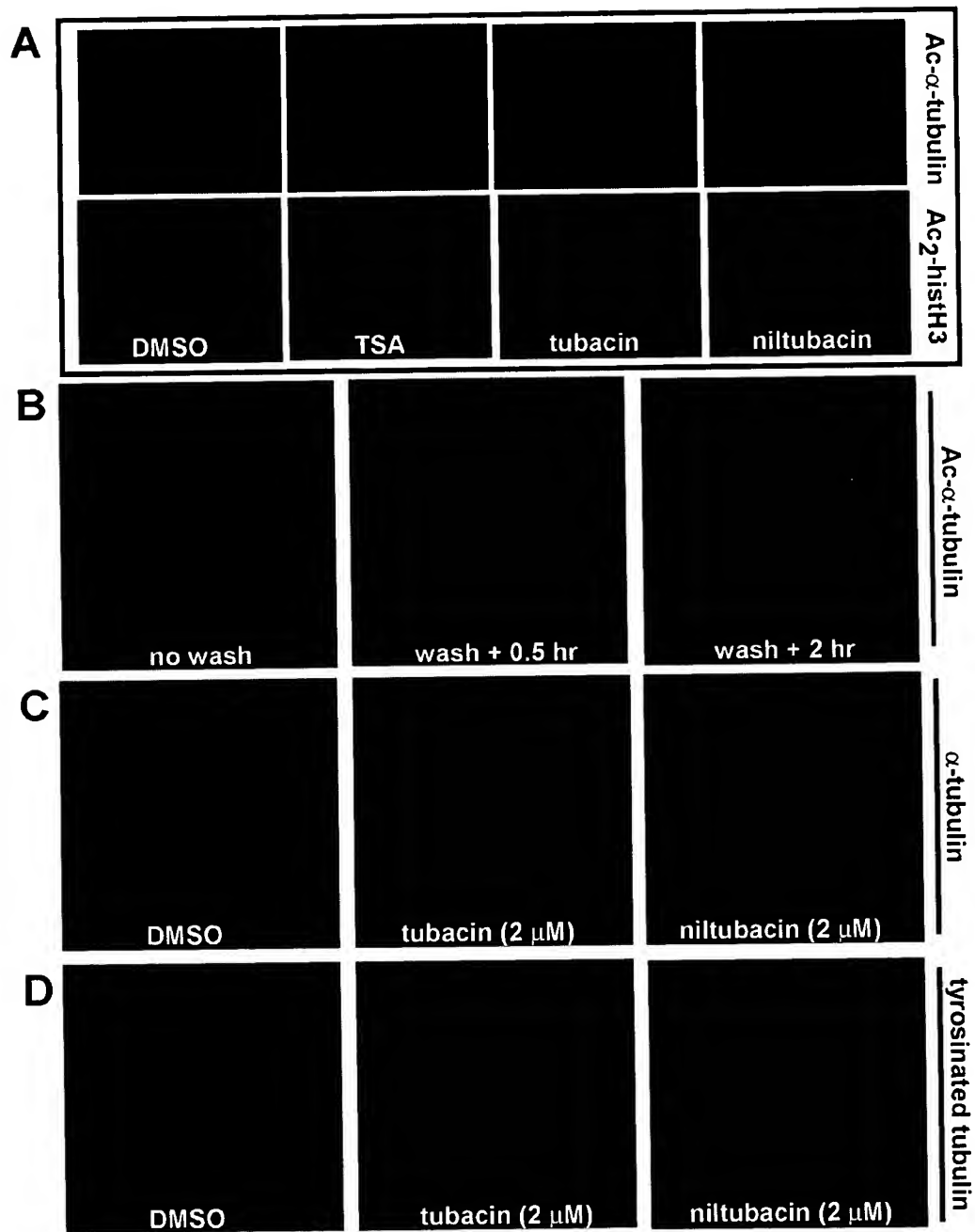
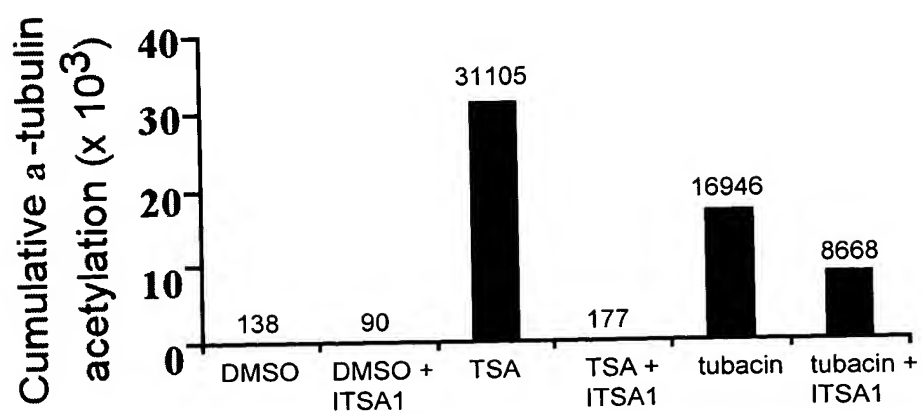
FIG. 46

FIG. 47A

Treatment	Mean α -tubulin acetylation
DMSO	92
ITSA1	82
TSA	322
TSA + ITSA1	104
tubacin	183
tubacin + ITSA1	110

FIG. 47B

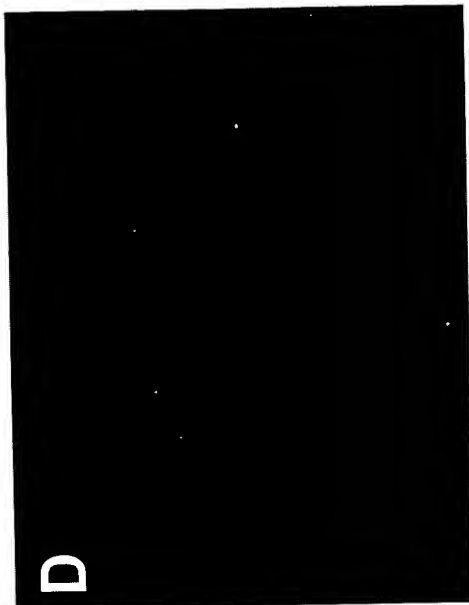


FIG. 47 D



FIG. 47 F



FIG. 47 C



FIG. 47 E

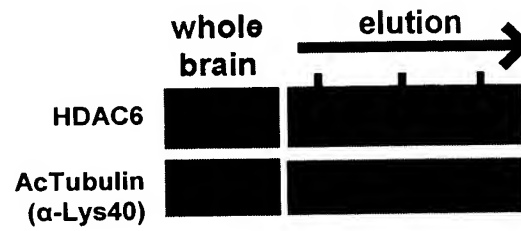
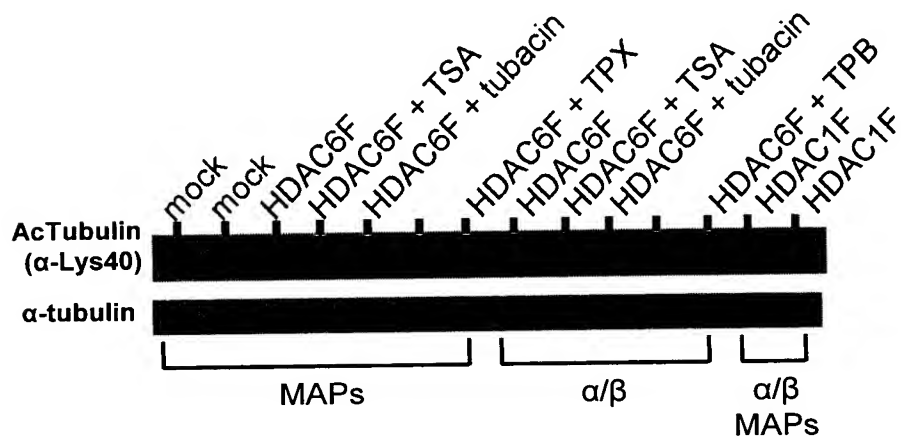
FIG. 47G**FIG. 47H**

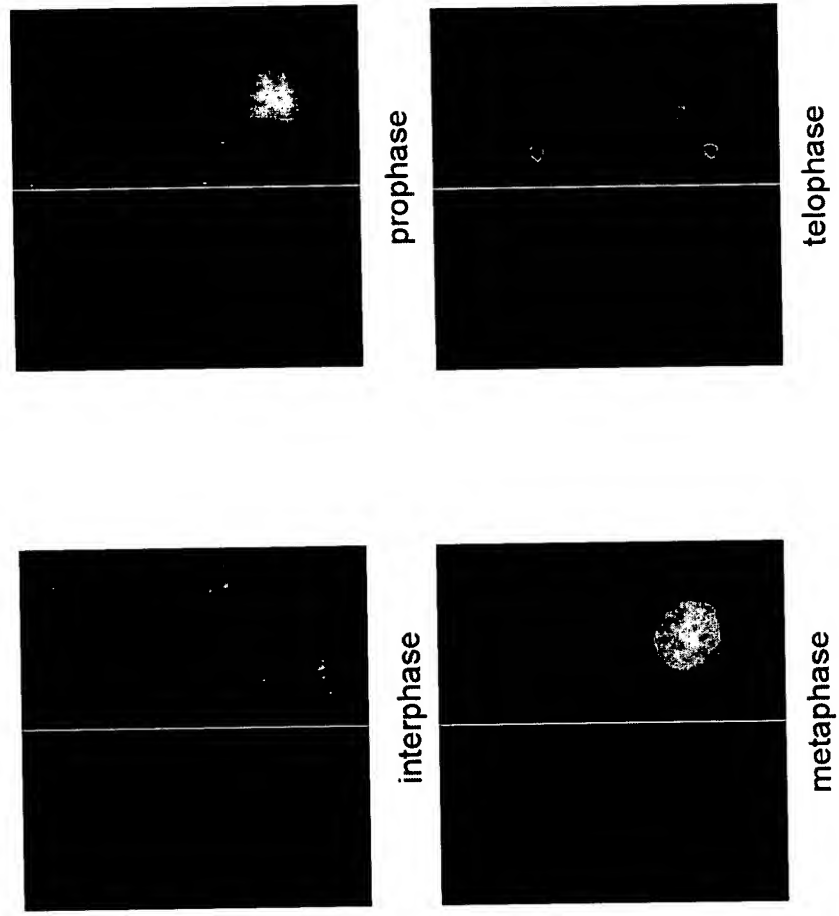
FIG. 48A

FIG. 48B

FIG. 49A

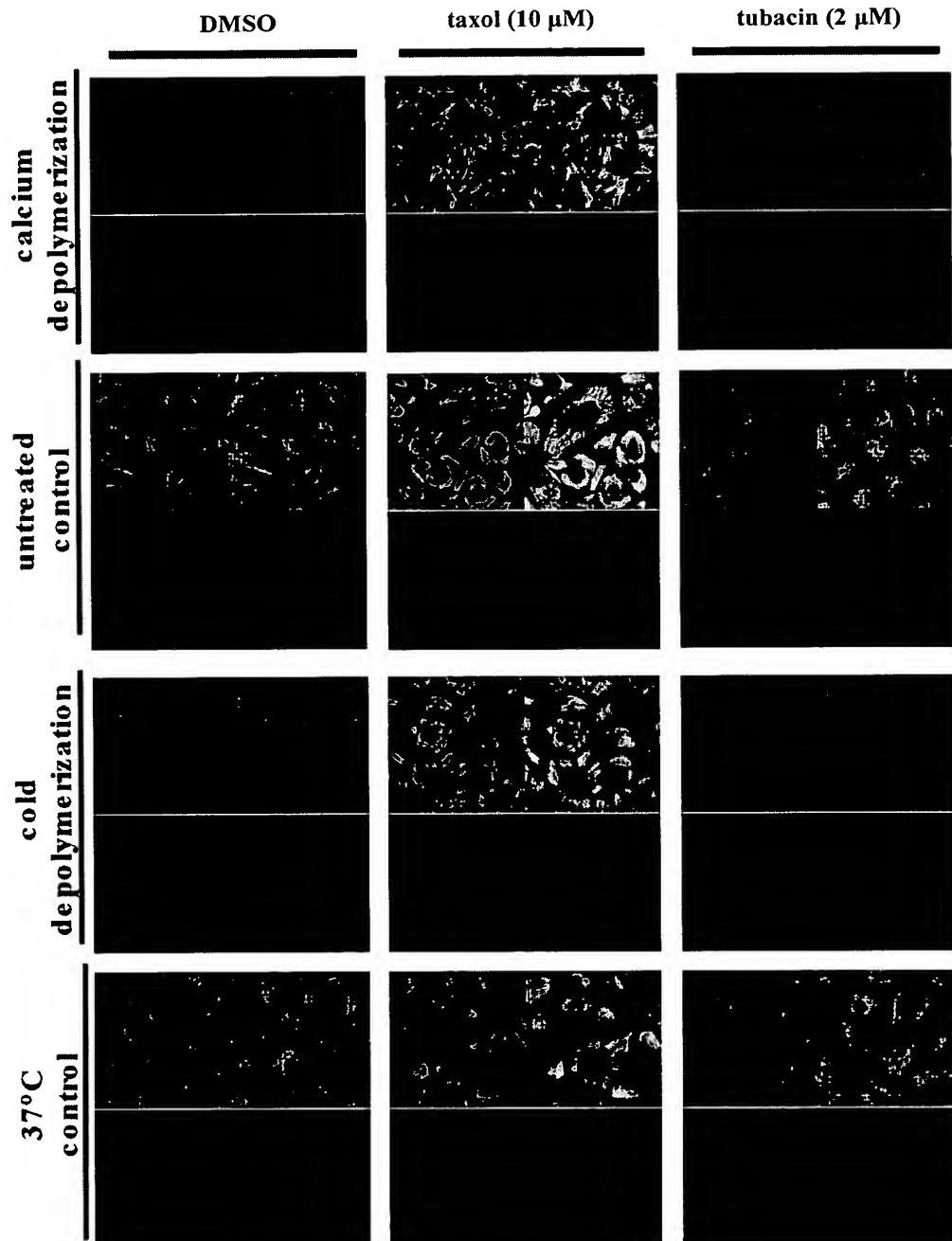


FIG. 49B

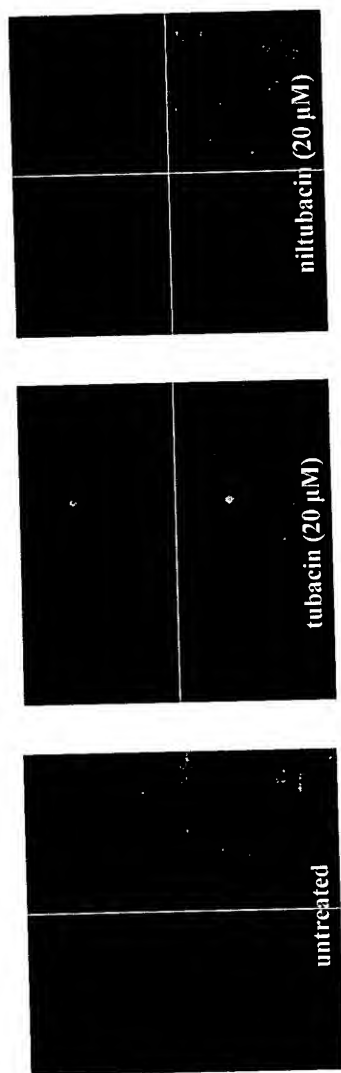


FIG. 49C

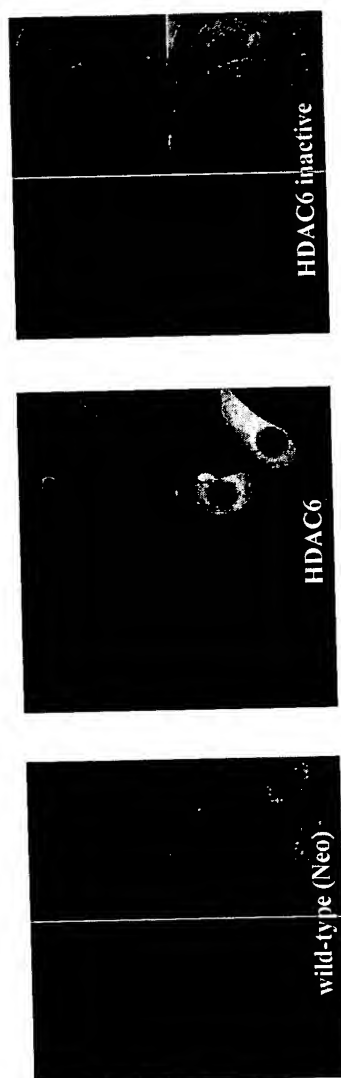


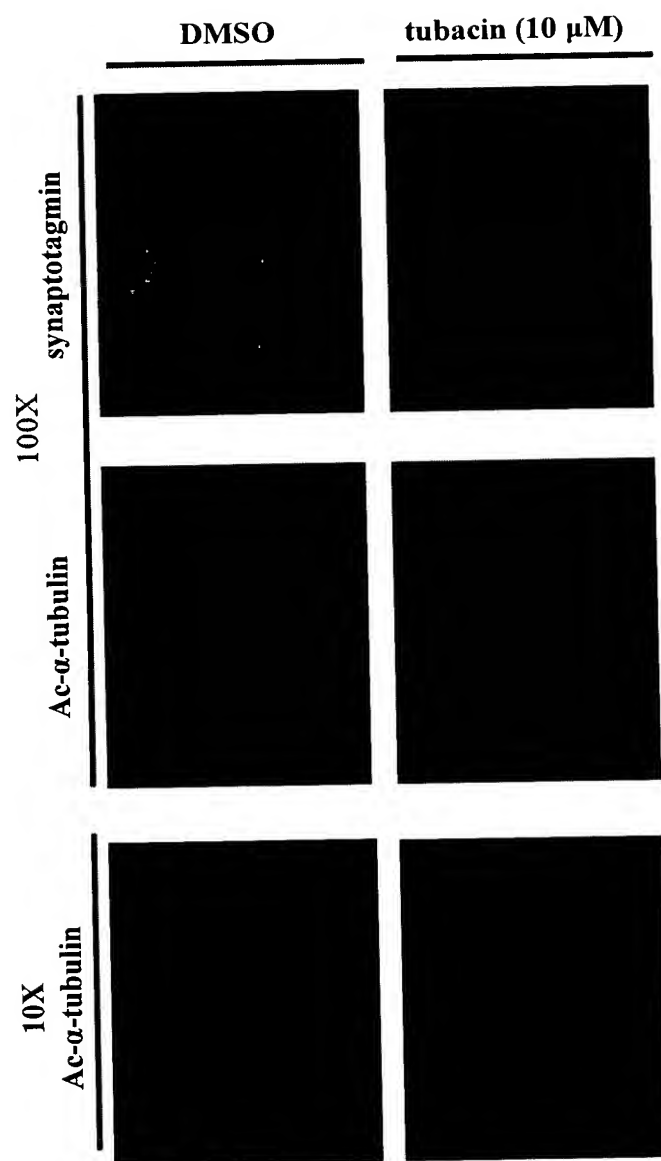
FIG. 50A

FIG. 50B

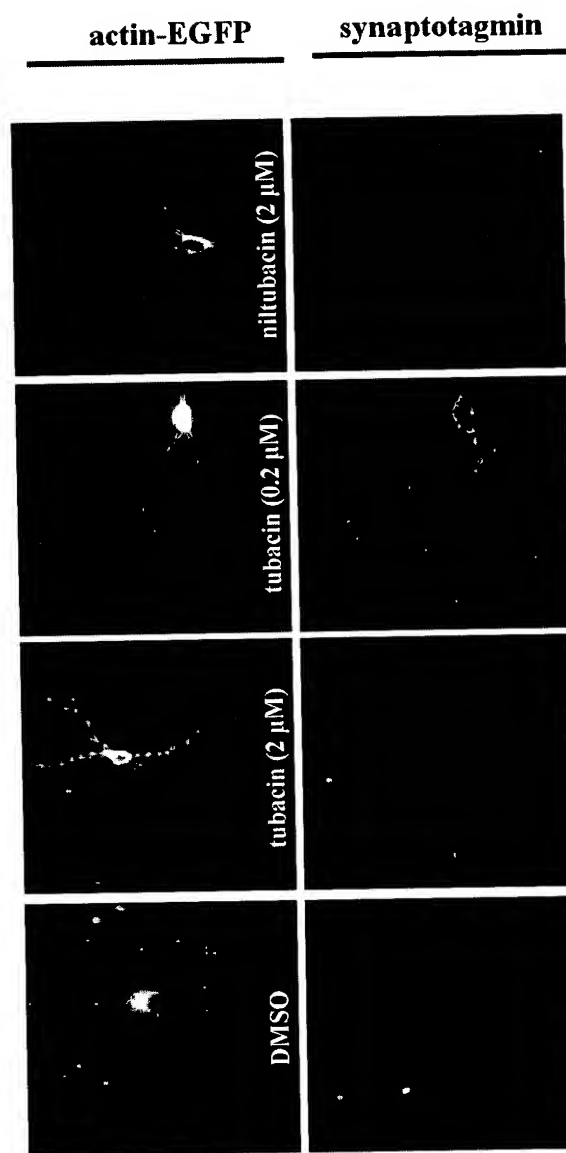
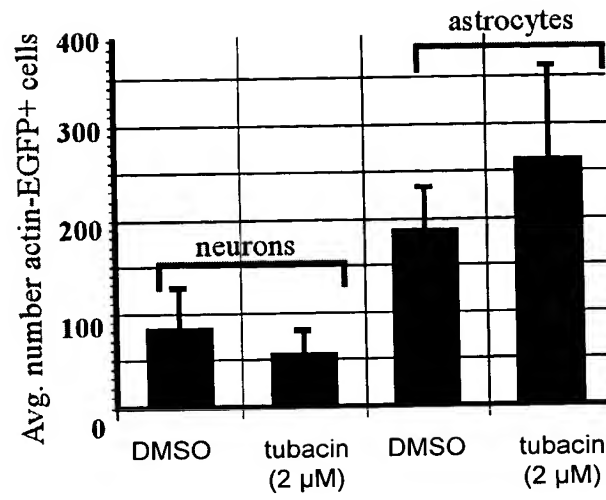


FIG. 50C**FIG. 50D**